Growth Hormone and Carbohydrate Metabolism

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The importance of the anterior pituitary gland in the regulation of carbohydrate metabolism has long been recognized. This relationship was shown by experiments[1] in which (1) hypophysectomy ameliorated the diabetes of depancreatized dogs, and (2) diabetes was induced by the administration of anterior pituitary extracts. Of the known anterior pituitary hormones, the part played by the adrenocorticotrophic hormone (ACTH) in carbohydrate metabolism via the adrenal cortex is well established.

The purpose of this paper is to present evidence that (1) an anterior pituitary hormone(s) other than ACTH plays a role in normal carbohydrate metabolism, and (2) most probably, this is growth hormone, or else some factor closely linked with it and as yet not separable.

METHODS

Trained and unanesthetized normal, adrenalectomized, adrenalectomized - gonadectomized, hypophysectomized, and adrenalectomized-hyophysectomized dogs were used. The animals were maintained in good condition on a mixed diet[2]. All adrenalectomized dogs (including those gonadectomized or hypophysectomized) were maintained on daily minimal doses of desoxycorticosterone acetate (DCA) in oil (Schering) 1.5—2.0 mg. per day intramuscularly unless otherwise stated.

All experiments were performed in the postabsorptive state, that is, 17-18 hours after the last food intake. Insulin sensitivity was determined by the response to 0.025 unit per kg. insulin (Lilly) administered intravenously. This has been designated as the "test dose". The glucose tolerance was determined by the response to an intravenous infusion of glucose, 0.075 gm. per kg. per min. for 10 min. In both types of tests, the blood sugar changes were followed at stated intervals over a 4-hour period.

The growth hormone preparations used were Armour preparations: lot Nos. 22KRI, J21609R and GH3; also Squibb preparation lot No. C515 was used. In addition, a growth hormone preparation was supplied by Dr. C. H. Li. The Armour and Squibb preparations were prepared according to the Wilhelmi method. The dosage varied from 0.02 to 2.0 mg. per kg. per day intramuscularly once daily. Growth hormone usually was administered after the afternoon feeding. The adrenocortical steroids, cortisone acetate or hydrocortisone acetate were given in daily dosages of 0.83—1.4 mg. per kg. intramuscularly in two divided doses (9 a.m. and 5 p.m.). Thyroxin (Roche-Organon), 0.25-0.52 mg. per kg. per day intramuscularly was given to hypophysectomized dogs. Some hypophysectomized dogs received whole thyroid, 600 mg. per day.

RESULTS

I. *The Insulin Sensitivity and Glucose Tolerance of Adrenalectomized, Adrenalectomized - Gonadectomized and Adrenalectomized-Hypophysectomized Dogs*

Figure 1 shows the response to the test dose of insulin of adrenalectomized dogs compared with that of normal and adrenalectomized-hypophysectomized dogs. The adrenalectomized dog maintained on DCA responds almost like a normal dog[3,4]. This is true, even when the DCA maintenance is withheld for periods of 8-14 days and signs of adrenal insufficiency supervene, so long as the animal being tested still is in the postabsorptive (17-18 hour fasted) state. Thus, removal of DCA has no effect upon the insulin response of adrenalectomized dogs. In

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contrast to this, the adrenalectomized-hypophysectomized dogs, on DCA maintenance, develop a precipitous fall in their blood sugar in response to the "test dose" of insulin which is followed in many cases by hypoglycemic convulsions [5,6,7]. This often necessitated a discontinuation of the experiment and institution of emergency treatment to save these dogs.

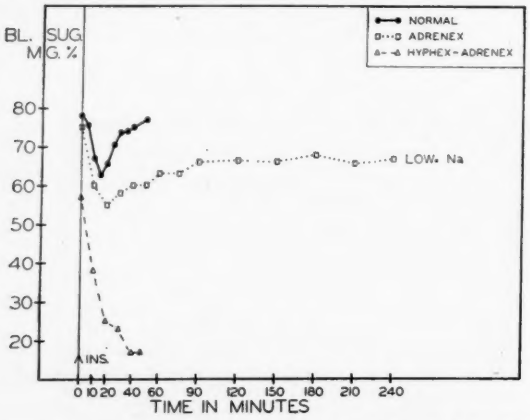

FIGURE 1. Composite blood sugar curves produced by insulin (0.025 u/kg. i.v.) in normal, hypophysectomized-adrenalectomized (hyphex-adrenex) dogs and adrenalectomized (adrenex) dogs, the latter during DCA-free periods. Courtesy of the "Annals of the New York Academy of Sciences."

In response to intravenous glucose the adrenalectomized dog manifests a secondary hypoglycemia, i.e., the blood sugar does not stabilize at the pre-infusion levels as it does in the normal dog, but rather falls below to hypoglycemic levels (Figure 2). Again, as with the insulin test, the adrenalectomized-hypophysectomized dog reacts more severely. The secondary hypoglycemia is more profound and frequently results in convulsions (Figure 2).

With regard to its responses to insulin and glucose, the adrenalectomized-gonadectomized dog reacts no differently than does the adrenalectomized-non-gonadectomized animal [6,7] (Figure 3).

COMMENT

From the above experiments (1) it is evident that an anterior pituitary factor(s) is responsible for the differences in carbohydrate metabolism (as judged by the responses to insulin and glucose) between adrenalectomized and adrenalectomized-gonadectomized dogs, on one hand, and adrenalectomized-hypophysectomized dogs on the other. (2) ACTH is not the factor being sought since it can be ruled out on the basis of its ineffective-

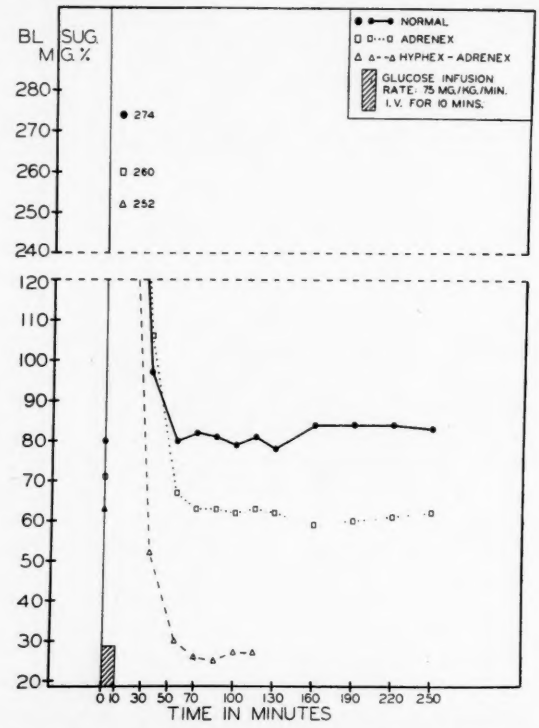

FIGURE 2. Composite blood sugar curves produced by intravenous glucose (0.75 g./kg.) in normal, adrenalectomized (adrenex) and hypophysectomized-adrenalectomized (hyphex-adrenex) dogs. Courtesy of the "Annals of the New York Academy of Sciences."

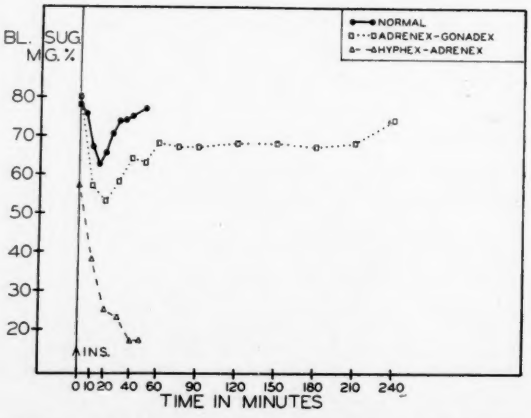

FIGURE 3. Blood sugar curve produced by insulin (0.025 u/kg. i.v.) in adrenalectomized-gonadectomized (adrenex-gonadex) dogs compared with those of normal and hypophysectomized - adrenalectomized (hyphex-adrenex) dogs. Courtesy of the "Annals of the New York Academy of Sciences."

ness in altering the insulin response of adrenalectomized dogs[8]. (3) Furthermore, the gonadotrophins also can be ruled out. (4) Moreover, the anterior pituitary factor in question can exert its action without the intermediation of either the adrenocortical or sex steroids.

II. *The Insulin Sensitivity and Glucose Tolerance of Hypophysectomized Dogs Before and During Cortisone or Hydrocortisone Regimens*

Further indirect evidence in support of the concept that an anterior pituitary hormone other than ACTH exerts an anti-insulin action in the normal animal was obtained from a series of experiments on hypophysectomized dogs treated with adrenocortical steroids. When such dogs received continued administration of either cortisone or hydrocortisone in dosages (0.83—1.4 mg. per kg. per day) sufficient to abolish the disturbances in carbohydrate metabolism of adrenalectomized dogs maintained on DCA, they still exhibited a greater insulin hypersensitivity than normal dogs as well as an abnormal glucose tolerance, that is the secondary hypoglycemia still was present[7,9]. Thus, although the steroids did ameliorate the disturbances in carbohydrate metabolism of the hypophysectomized dogs, they did not restore them to normal as they had in the adrenalectomized dogs. In other words, steroid replacement therapy showed that an anterior pituitary factor still was lacking in the hypophysectomized animals, and it was not ACTH.

III. *Effects of Thyroxin or Thyroid on the Insulin Hypersensitivity of Hypophysectomized Dogs*

The influence which thyrotrophin might have in the control of carbohydrate metabolism was then investigated. Thyrotrophin preparations were not used inasmuch as they contained significant amounts of several other anterior pituitary hormones which might thus have confused the interpretation of any positive results obtained.

With this in mind, whole thyroid or thyroxin was administered to hypophysectomized dogs in dosages which eventually produced signs of clinical hyperthyroidism (increased irritability, increased heart rate, loss of weight, rise in body temperature). However, the effect upon the insulin hypersensitivity of these dogs was slight [6,7]. Thus, thyrotrophin also was ruled out as the possible factor being sought. Of the remaining anterior pituitary hormones, only growth hormone and prolactin had to be considered.

IV. *Effects of Growth Hormone on the Insulin Hypersensitivity and Glucose Tolerance of Hypophysectomized Dogs*

Growth hormone (Armour), when administered in a dose of 1.0 mg. per kg. intramuscularly to the postprandial hypophysectomized dog, will produce a significant diminution in the dog's exaggerated response to insulin; this is in evidence when the animal in the postabsorptive state is tested 17-18 hours after the injection of growth hormone. After 3 or 4 days of such a growth hormone regimen (1.0 mg. per kg. per day), the insulin hypersensitivity usually is completely abolished[2, 10, 11] (Figure 4). However, concomitantly, a diabetic glucose tolerance (Figure 5) and a resistance to even large doses of insulin always develop[2]. No glycosuria or acetonuria has been observed in such a growth hormone-treated hypophysectomized dog, although toxic manifestations (anorexia, nausea, vomiting, lethargy) have appeared during the regimen and, occasionally, death of the animal has occurred. Similarly, growth hormone will produce abolition of the insulin hypersensitivity of adrenalectomized-hypophysectomized dogs[5,6,12], thereby ruling out the possible influence of the ACTH contamination of the growth hormone preparation. In addition, such an action, when obtained in adrenalectomized-hypophysectomized dogs, rules out the essentiality of the adrenocortical steroids for the production of a growth hormone effect.

Although growth hormone has potent effects on carbohydrate metabolism, its diabetogenic action can be of little physiological significance unless it can be shown that growth hormone antagonizes the hypoglycemic action of insulin and thus raises the blood sugar in physiological life without producing diabetes. If this is true,

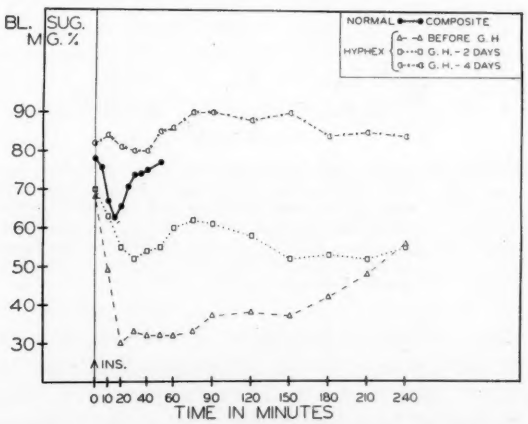

FIGURE 4. Blood sugar curves produced by insulin (0.025 u/kg. i.v.) in a typical hypophysectomized dog before and during growth hormone regimen compared with that of normal dogs. Armour growth hormone #22KRI, 1 mg./kg./day, administered. Insulin tests performed after 2 and 4 doses of growth hormone.

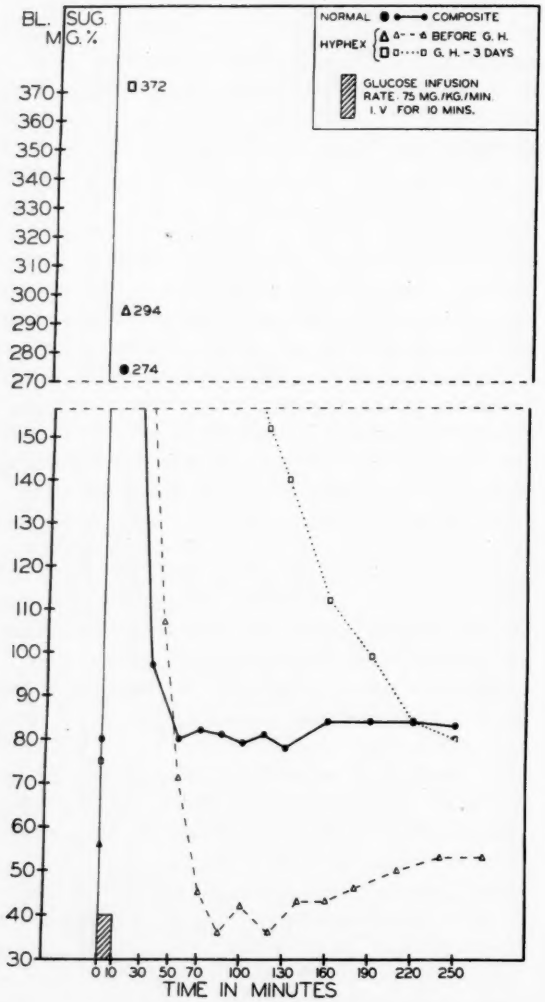

FIGURE 5. Blood sugar curves produced by intravenous glucose (0.75 g./kg.) in a typical hypophysectomized dog before and during growth hormone regimen compared with that of normal dogs. Armour growth hormone #22KR1, 1 mg./kg./day administered. Glucose tolerance test performed after 3 doses of growth hormone.

then it should be possible to demonstrate, with the proper dosages and under the proper conditions, that growth hormone will ameliorate the exaggerated insulin response of hypophysectomized dogs without inducing diabetes. Furthermore, such an effect, when once obtained, should continue indefinitely without incident during the administration of the hormone. Only then could growth hormone be considered to have some physiological importance in carbohydrate metabolism.

With this objective in view and using the same Armour preparation, the growth hormone dosage was reduced from 1.0 to 0.3 mg./kg./day[6]. While this reduction delayed, it nevertheless resulted in the development of diabetes or toxicity. Even when growth hormone was administered in the smallest effective dosages, 0.02 mg./kg./day, a diabetic tendency eventually appeared in about 50 per cent of the dogs[5,6]. These studies were concluded because the animals in time (after 30-40 days administration) became resistant to the growth hormone action. (It should be emphasized that 0.02 mg. per kg. per day is about 1/10 the amount of growth hormone needed to produce measurable growth in hypophysectomized rats).

In another series of experiments, prolonged administration of large doses of growth hormone (1.0-1.5 mg. per kg. per day) to hypophysectomized dogs was made possible without the production of either diabetes, insulin resistance, or toxicity. This was accomplished by combining the growth hormone regimen with an adrenocortical steroid regimen[5,6,13]. Figures 6 and 7 illustrate the responses to insulin and glucose, respectively, of hypophysectomized dogs that first received cortisone or hydrocortisone therapy and subsequently, a combined steroid-growth hormone regimen. It will be noted that the steroid regimens alone only ameliorated the disturbances

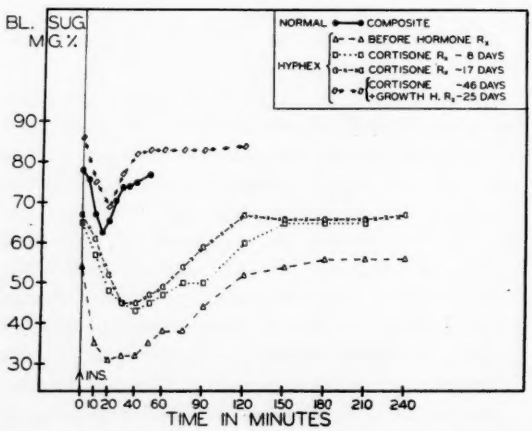

FIGURE 6. Blood sugar curves produced by insulin (0.025 u/kg. i.v.) in (a) normal dogs and in a typical hypophysectomized dog (b) during the untreated state, (c) during cortisone regimen alone and (d) during a combined cortisone-growth hormone regimen. Cortisone, 1.0 — 1.4 mg./kg./day, given for a total of 46 days. Squibb growth hormone #C515, 1.0 — 1.5 mg./kg./day, begun on the 22nd day of cortisone regimen and continued for 25 days.

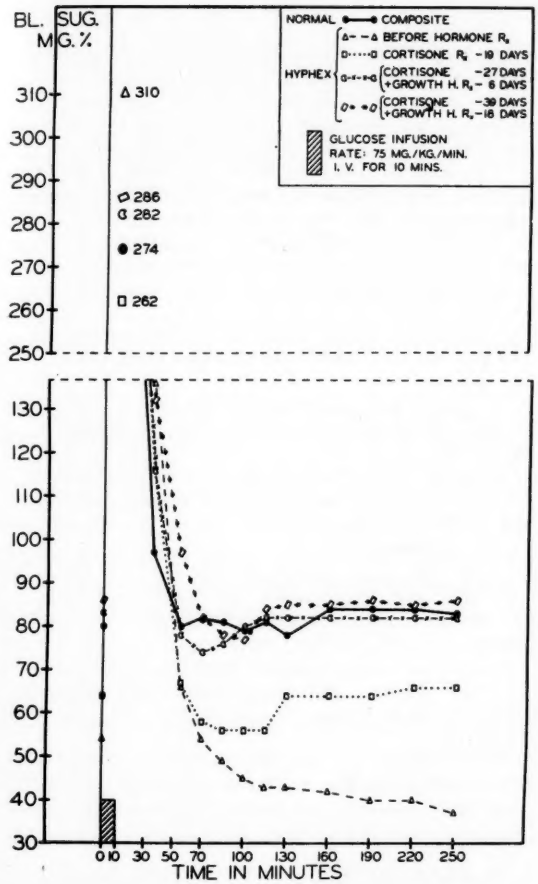

FIGURE 7. Blood sugar curves produced by intravenous glucose (0.75 g./kg.) in (a) normal dogs and in a typical hypophysectomized dog (b) during the untreated state, (c) during cortisone regimen alone and (d) during a combined cortisone-growth hormone regimen. Cortisone, 1.0 — 1.4 mg./kg./day, given for a total of 39 days. Squibb growth hormone #C515, 1.0 mg./kg./day, begun on the 22nd day of cortisone regimen and continued for 18 days.

in carbohydrate metabolism of the hypophysectomized dog[9]. On a combined hormonal regimen, however, the responses both to insulin and glucose became normal and remained so throughout the prolonged therapy[5,6,13]. No toxic manifestations were observed.

Thus far, attempts to administer the growth hormone regimen first and then follow it with a combined growth hormone-steroid regimen have proved to be unsuccessful. With such an order of administration, the hypophysectomized dogs were not able to tolerate the growth hormone (in view of its toxicity) so that several animals died before the adrenocortical steroid therapy could be given in conjunction with the growth hormone.

DISCUSSION

From the above experiments, it is apparent that the adrenalectomized dog has a functioning anterior pituitary hormone (probably growth hormone or some other factor closely linked with it) which exerts an anti-insulin action in the absence of the adrenocortical steroids and does not produce any toxic manifestations. This anti-insulin action is sufficient to protect the adrenalectomized dog against very small doses of insulin (e.g., 0.025 unit/kg.) but not against larger doses (namely 0.25 unit/kg.). Administered growth hormone also produces potent effects (not due to ACTH) in the absence of the adrenocortical steroids as shown by its action in adrenalectomized-hypophysectomized dogs. However, such administration eventually results in the production of diabetes, insulin resistance and/or toxicity. This is true even for the smallest effective dose used, 0.02 mg. per kg. per day intramuscularly. These untoward manifestations of growth hormone administration are eliminated if C-11, 17-oxycorticosteroid therapy precedes and then accompanies the growth hormone regimen in the hypophysectomized dog. Indeed, a normal carbohydrate metabolism results. Under these conditions, large doses of growth hormone (1.0-1.5 mg. per kg. per day intramuscularly) can be administered safely for prolonged periods of time.

Since such optimum effects were achieved with combined growth hormone-adrenocortical steroid regimens, these experiments suggest that a delicate balance exists between these two hormonal factors which enables growth hormone to participate effectively in the regulation of carbohydrate metabolism.

At present, our knowledge of the mechanisms of action of the steroids and growth hormone is insufficient to explain the above findings produced by a combined hormonal regimen. The adrenocortical steroids and growth hormone both antagonize the action of insulin and are either potentially or actually diabetogenic, the former, primarily by enhancing gluconeogenesis[14,15] and possibly interfering with the peripheral utilization of sugar[16,17,18,19] and the latter hormone, by inhibiting peripheral utilization [2,20,21,22]. Yet both, in combination, did not produce a summation or potentiation of their respective effects. It is evident therefore, that the interplay between these two hormonal agents still awaits elucidation.

In addition to growth hormone and its effect on car-

bohydrate metabolism, experiments in progress with adrenalectomized-hypophysectomized dogs have revealed that prolactin can exert an anti-insulin action which is not due to the ACTH contaminant[12,23]. Likewise, heated prolactin can exert an anti-insulin action, thereby ruling out the growth hormone contaminant[12,23]. Thus, the role of prolactin, if any, in carbohydrate metabolism still awaits clarification.

SUMMARY AND CONCLUSIONS

1. An anterior pituitary factor other than ACTH exerts an anti-insulin action in the adrenalectomized dog. It is not thyrotrophin nor the gonadotrophins. 2. It can exert its action in the absence of the C-11, 17-oxycorticosteroids and sex steroids. 3. Most probably this factor is the growth hormone or a hormone intimately linked with it. The ACTH content of growth hormone preparations is not responsible for the actions in carbohydrate metabolism attributed to the growth hormone, nor are the adrenocortical steroids absolutely essential for its action(s). 4. Administered growth hormone exerts a potent anti-insulin action in hypophysectomized dogs, but concomitantly produces diabetes, insulin resistance and toxicity. 5. Administered growth hormone can be given for extended periods of time without producing diabetes, insulin resistance, and/or toxicity when given in conjunction with C-11, 17-oxycorticosteroid regimens. A normal carbohydrate metabolism is produced in hypophysectomized dogs treated with such combined hormonal regimens. 6. Thus, it appears that in physiological life, growth hormone acts in concert with the adrenocortical steroids in the endocrine control of normal carbohydrate metabolism.

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Group discussion of this paper and that by Dr. Ephraim Shorr and his associates follows after the next paper

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The Relation of Chronic Disease to Diet

A challenging problem for the nutritionist is the fact that physicians, who so often ascribe acute illness to a recent dietary mishap, have always hated to accept any theory ascribing chronic disease to bad food. Thus, the causation of scurvy was clearly and convincingly described by Bachstrom in 1743; lemon juice as a preventive and cure, with excellent resistance to storage, was recommended in Lind's treatise in 1754. A critical test was given by the British navy in 1795, the year of Lind's death, and the brilliant success led to the orders which abolished scurvy forever from British ships. Thanks to Lind's work, Nelson's sailors enjoyed unusual health during the decades when his "distant storm-tossed ships" stood between Napoleon and the conquest of the world.

In 1908 Holst and Frohlich found that the guinea pig, alone among domestic or laboratory animals, developed scurvy on diets like those of the sailors before 1800, and could be cured by lemon juice. This test animal later served to control the isolation and synthesis of ascorbic acid (Vitamin C). But all this left the medical profession cold. For a decade after Holst's work, and a century and a quarter after the Lords of the Admiralty accepted Lind's theories, the *Encyclopedia Britannica* and leading medical texts disparaged the dietary theory and spoke favorably of "infection by an unknown microbe." In 1950 a text widely used by English-speaking students of medicine stated that "young men totally deprived of Vitamin C, but leading an active life with outdoor exercise, have not developed any symptoms or signs of scurvy over prolonged periods." Thus two centuries after Bachstrom's studies and twenty years after Szent-Gyorgy identified the chemical nature of the missing substance in scorbutic diets, a distinguished internist found the theory so distasteful that he allowed himself to forget that sailors who died of scurvy had been young men getting 12 to 20 hours daily of "active outdoor exercise" on the decks and in the rigging of their ships and that lemon juice had promptly cured every symptom and sign.

The story of scurvy is now being re-enacted in the history of atherosclerosis and the effect of excessive dietary cholesterol.

Since two centuries of practical and experimental study have failed to convince some physicians that diets of salt pork, beans, and flour may be inadequate for maintaining health, it probably will take a long time to convince the profession that diets rich in eggs, butter and cream cause the disease which now kills nearly one out of every three physicians. The biologist knows that such diets are as alien to adult mammals as those which cause scurvy, beriberi, and pellagra.

The nutritionist may fail to correct this type of abnormal diet, but industry will find it profitable to have those who use these foods add sitosterols or dihydrocholesterol[1] to the diet. These substances block cholesterol absorption, and prevent both hypercholesterolemia and atherosclerosis in the experimental animal.

Thus, by a slight increase in cost of his foods, man may learn to eat cholesterol and not absorb it.

From an editorial entitled "The Reluctance of Physicians to Admit That Chronic Disease May be Due to Faulty Diet," by William Dock, M.D., in *The Journal of Clinical Nutrition*, March-April 1953.

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Metabolic Studies on the Effects of Crystalline Growth Hormone (Somatotropin) in Man

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In contrast with the rich literature on the effects of growth hormone (Somatotropin) in animals, evidence of its action in man is scant and inconclusive. This stems in large measure from the unavailability, until recently, of sufficient amounts of Somatotropin to provide for adequate studies in the human. It was not until 1948 when Wilhelmi, Fishman and Russell had developed a procedure for crystallizing growth hormone in good yield, that a wider exploration of its biological properties in man was made possible. The data on human subjects obtained since then are in conflict as to whether this hormone can achieve in man the effects which it produces in animals.

The present report is a summary of the data obtained on 2 of 5 human subjects studied during the past 5 years while receiving crystalline Somatotropin prepared by the Armour Laboratories according to the method of Wilhelmi, Fishman and Russell. They were studied in the Research Metabolism Ward of the Russell Sage Institute of Pathology while on diets constant for each subject with respect to calories, carbohydrate, fat, protein, calcium and phosphorus intake. The data are related to the effects of Somatotropin on the storage of nitrogen, calcium and phosphorus and the levels of serum calcium, inorganic phosphorus and alkaline phosphatase.

The first patient, L. F., was 14 years, 7 months old at the start of the study, with a bone age of 10 years, 9 months. Her height was 136.6 cm., her weight 29.3 kg. Her linear growth had been slow since the age of 2. There was no evidence of thyroid or adrenal insufficiency except for mild insulin sensitivity. She had not as yet menstruated. A 9-week control period on a constant dietary intake provided the baseline data for the evaluation of the effects of Somatotropin. The diet was such that she was on positive balance with respect to protein, calcium and phosphorus. Crystalline Armour Somatotropin was administered over a period of 11 weeks. The daily dose averaged 120 mg. with a maximum of 300 mg. per day. There was a prompt anabolic effect on nitrogen metabolism which was maximal in the third week during which 15 gm. of nitrogen were stored. This was followed by a decline and then a fall below the baseline with a subsequent return of an anabolic effect of lesser magnitude. A similar increase in phosphorus storage occurred with fluctuations which paralleled those for nitrogen storage. Increased retention of calcium occurred during

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We are indebted to the Armour Laboratories, Chicago, for the Somatotropin used in these studies.

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the first three-week period and persisted with minor fluctuations throughout the period of administration. After Somatotropin was stopped there was a sharp augmentation of nitrogen and phosphorus storage and a persistence of the enhanced storage of calcium. All values returned to the control levels 7 weeks after stopping treatment.

During Somatotropin administration serum inorganic phosphorus levels fell slightly below the baseline values by an average of 0.3 mg. per 100 cc. Alkaline phosphatase rose slightly on the average of 0.7 of a Bodansky unit, then fell below control values. After stopping Somatotropin, alkaline phosphatase rose to a maximum of 12.8 Bodansky units 6 weeks after.

The glucose tolerance curves became progressively more diabetic during Somatotropin therapy with the eventual development of a frank glycosuria which disappeared promptly on stopping therapy. Appreciable increase of insulin resistance also developed at the end of the treatment period. On discontinuation of Somatotropin, the oral glucose tolerance curves reverted towards the control values.

The second patient, R. V., was 17 years and 10 months old when the study was begun. She had a bone age of 11 years and 3 months. Her height was 124.8 cm., her weight 25.7 kg. Linear growth had been delayed since the age of 2. She had no secondary sexual characteristics and had never menstruated. She was receiving 112 mg. of desiccated thyroid daily for demonstrated thyroid insufficiency. During the period prior to receiving thyroid and while being thyroid insufficient, Somatotropin was given without any anabolic effect on nitrogen, calcium and phosphorus metabolism. She was studied for 2 years under adequate thyroid replacement therapy with several lots of Somatotropin (Armour) and one lot of Somatotropin supplied by Raben and Westermeyer. Somatotropin (Armour) achieved anabolic effects in this patient which were less pronounced than in the first patient. That of Raben and Westermeyer was without anabolic effect.

Three separate courses of Armour's Somatotropin were given. The third course for a period of 3 weeks (averaging 206 mg. daily) was associated with the most pronounced enhancement of nitrogen, calcium and phosphorus storage. This third course of treatment was also accompanied by a gradual rise in the blood sugar levels during oral glucose tolerance tests as well as the development of increased insulin resistance. This last course of therapy was also followed by a persistence of the anabolic effects on protein, phosphorus and calcium metabolism for a period of 9 weeks after discontinuation of therapy. In this interval there was a return of the oral glucose tolerance tests and insulin sensitivity to control values. The magnitude of the anabolic effects of Somatotropin are summarized in the following table:

Magnitude of Somatotropin effect
on nitrogen, calcium and phosphorus metabolism

Patient	Total Somatotropin gm.	Duration of		Total "extra" retention of		
		Treatment weeks	Action weeks	Nitrogen gm.	Calcium gm.	Phosphorus gm.
L.F.	9.38	11	18	149.5	17.2	13.7
R.V.	3.45	3	14	78.8	11.4	17.0

Three young males (aged 15, 15, and 13 years) of short stature but with no associated endocrine abnormalities failed to respond to various Somatotropin preparations, some of which produced anabolic effects in the 2 subjects described above.

SUMMARY

Somatotropin prepared by the Armour Laboratories according to the method of Wilhelmi, Fishman and Russell was administered to 2 subjects, both females of abnormally short stature, who were maintained under a constant dietary regime throughout the study. In both, enhanced storage of nitrogen, calcium and phosphorus was achieved as well as anti-insulin effects consisting of impaired glucose tolerance and increased resistance to insulin. These latter defects reverted to the pretreatment states after Somatotropin was discontinued. Three boys with short stature failed to exhibit any of the above metabolic responses to Somatotropin. These findings in man are confirmatory of similar actions of Somatotropin previously reported to occur in the dog and cat.

GROUP DISCUSSION OF PAPERS ON GROWTH HORMONE BY DRS. DE BODO, SHORR AND ASSOCIATES

F. D. W. LUKENS, M.D., (*Philadelphia*): Both Societies are privileged to hear Drs. de Bodo, Kinsell and Shorr present some of the current work on growth hormone. Physicians are quick to ask: Why is this relatively pure preparation highly potent in animals but ineffective in man? From the three speakers on these programs I cull the following facts which appear related to this question, and summarize the facts, subject to the correction of the speakers.

Many so-called pure preparations of growth hormone have inflammatory or toxic effects. Dr. de Bodo described these in hypophysectomized animals but not in normal animals, or animals treated with cortisone. Both Drs. Kinsell and Shorr have reported local and systemic toxic reactions in man in their past trials of growth hormone. It is also recognized that purified growth hormone still contains significant amounts of thyrotrophin. This would lead one to conclude that either toxic impurities or hormonal contamination, or both, might be responsible for the failure of growth hormone to act in man. Dr. de Bodo neutralized the toxic effects by the simultaneous administration of cortisone. Drs. Kinsell and Shorr avoided toxic effects by the use of new and different preparations. In this connection, I would ask Dr. de Bodo whether his combination of growth hormone and cortisone permitted nitrogen retention? If it did, it would differ from Dr. Kinsell's results with ACTH and growth hormone.

This morning (at the meeting of The Endocrine Society) Dr. Kinsell reported that nitrogen retention occurred in a hypothyroid patient in whom the growth extract caused no pyrexia. Does he attribute this result to the avoidance of the action of thyrotrophin or to the lack of fever? Has he used the same non-toxic preparation in a euthyroid patient? In this connection, Dr. Shorr might like to comment on the euthyroid patients in whom he observed nitrogen retention.

The best conclusion that I can reach from these three excellent reports is that some toxic contaminant of growth hormone has in the past prevented us from observing its usual effects in man and that we have at these meetings received the first suggestion that this dificulty may be overcome in the near future.

LAURANCE W. KINSELL, M.D., (*Oakland, Calif.*): If I may, I shall discuss the remarks of the discusser first, and then proceed from there.

The matter of pyrogenicity was raised by Dr. Lukens. During the past two years, we have not encountered pyrogenicity with any preparation used, with or without the use of any other hormonal factor, that is, with or without the co-administration of ACTH or cortisone. It would, therefore, appear that the pyrogenicity was in all likelihood referable to denatured protein material in some of the earlier preparations; that appears, we hope, to be a problem of the past.

Second, in the report of a "positive growth effect" which my associates and I presented this morning before The Endocrine Society, this protein anabolic effect was obtained in a patient who had no functioning thyroid tissue. We can only wonder whether the positive effect in this patient was obtained because she lacked thyroid tissue; did the fact that no thyroid was present to respond to the thyrotrophin contaminant, permit us to obtain a true growth hormone effect? This lot of growth hormone was not available in sufficient amount for use in a euthyroid patient.

It would appear that perhaps there is a little light beginning to show on the horizon and that one of these days we may have a preparation which will have true clinical usefulness. The fact that all preparations which are thus far available have the property of diabetogenesis obviously raises certain real and potential problems, from the standpoint of clinical use.

I should like to discuss the results of a study still in process, of which a portion is completed, to illustrate intensification of the diabetic state in a patient with spontaneously occurring diabetes during the administration of pituitary growth hormone.

This diabetic patient received a constant dosage of insulin and a chemically constant diet throughout. Growth hormone was administered by intravenous infusion over a period of 12 hours in each 24-hour period during six days. Observations of the nitrogen, sodium and potassium balance, as well as the body weight of the patient were for periods of six days' control, six days' treatment, and six days' post-treatment. The same intravenous infusion of mixed sodium and potassium solution was given throughout, so the only variable was the growth hormone. There was a considerable increase in sugar excretion in the urine as well as a very slight net increase in nitrogen excretion, slight net retention of sodium which continued after the material was stopped, probably significant, and essentially no change in potassium.

Observations were also made, in the same case, of sugar, urinary sugar, blood ketones, urinary ketones, 17-ketosteroids and circulating eosinophils. During and following growth hormone administration, there was a net daily increase of approximately 40 gm. of sugar in the urine. This was associated with a comparable increase in the average blood sugar value. This diabetogenic effect continued for six days after the growth hormone preparation had been stopped; the blood ketones changed very little indeed; the urinary ketones increased slightly.

These slight changes in ketones are in sharp contrast to the picture that one obtains in a diabetic who receives either ACTH or cortisone under these ex-

perimental conditions. There was a slight increase in 17-ketosteroids, a slight fall in the eosinophils, perhaps of a magnitude that one would obtain by administration of a half to one unit of ACTH by slow intravenous infusion, a negligible amount. I think one can be reasonably certain that the diabetogenic effects were not, in the main at least, due to contamination with a small amount of ACTH. The patient was slightly hypothyroid, the test with radioactive iodine showed 13 per cent uptake initially, 34 per cent, at the end of six days' treatment, and still the same value after six day's post-treatment. Also of interest was a rise in the respiratory quotient from a normal level. When one gives ACTH to a diabetic, exactly the opposite occurs; the respiratory quotient falls strikingly.

In conclusion one might say that in humans, the picture follows very much the same pattern as in animals, or at least it is beginning to. There is a major question, as Dr. de Bodo indicated, as to whether this diabetogenic property of growth factor is an inherent property of the material itself, or something that is still going along for the ride, so to speak, in a chemical sense. One would hope that the latter is the case, and that eventually we will have an agent which is purely anabolic. One more thought would be—what if this is a separate diabetogenic factor? What is its function, and how does it work? From the RQ findings and the other observations one would be left with the concept that it must produce its effect by actually inhibiting the utilization of glucose rather than by stimulating neoglucogenesis.

Dr. de Bodo's findings with cortisone certainly open up a most interesting vista for further work.

A QUESTIONER: I should like to ask what is the effect of growth hormone on liver glycogen?

CHESTER SOLEZ, M.D., *(Narraganset, R. I.)*: Cortisone is usually considered diabetogenic, but one of the speakers spoke as if it were antidiabetogenic. How is such effect explained?

RICHARD C. de BODO, M.D., *(New York, N.Y.)*: In answer to Dr. Lukens, I should like to recall the statement made at the beginning of our paper, namely, that the animal's own anterior pituitary factor (most probably growth hormone) which is responsible for the anti-insulin action certainly is not toxic. This toxicity was observed only when growth hormone preparations were administered. All the preparations used were toxic in varying degree.

The cause of this toxicity is as yet unexplained. It is our impression that the severity of the toxicity parallels the diabetogenic potency of the preparation used. We don't think that the toxicity is due to the TSH contaminant in the growth hormone preparations since the thyroid glands remained atrophic in such growth hormone-treated animals.

Before answering Dr. Solez' question, I should like to add this prefatory remark. The primary reason for working with hypophysectomized animals is our interest in the physiological significance, if any, of growth hormone in carbohydrate metabolism. Thus, we use an animal that has no growth hormone and very atrophic adrenal cortices, viz., the hypophysectomized dog. The administration of the combined steroid-growth hormone regimen in such an animal is an attempt to provide a truly adequate hormonal replacement therapy. It is not surprising therefore, although both the steroids and growth hormone are "diabetogenic," that a normal metabolism is the result under such experimental conditions.

The relationship of growth hormone to the steroids is not clear. Indeed, it is still not known whether growth hormone *in vivo* undergoes a transformation to another effective agent or whether it liberates another substance. In either case, it is possible that the steroids in some way modify the actions of this agent(s).

As to the previous question, viz., whether growth hormone has any effect on liver glycogen, I really could not say. We do know that muscle glycogen is increased. Since the hypophysectomized animal has a decreased gluconeogenesis due to the adrenocortical atrophy and since growth hormone, by virtue of its protein-synthesizing action further limits gluconeogenesis, I should expect that the liver glycogen would be decreased.

EPHRAIM SHORR, M.D., *(New York City)*: As to the questions that Dr. Lukens raised of toxic reactions, I think, with Dr. Kinsell, that a large number of them can be attributed to some type of denaturization of protein. We have been very fortunate in the materials that we have received from the Armour Laboratories, which have been used, as you could have seen from the chart, for long periods of time without febrile reactions, except for an occasional instance, generally associated with a local reaction to the injection.

Induration will occasionally appear with a brief febrile reaction, which subsides the next day; but by and large, the whole course of study has been relatively free of the type of febrile reactions that we have seen

reported, particularly with the use of the highly purified hormone.

I think the discrepancies between the results in different laboratories with some of the earlier preparations may find their explanation in the differences in the period of time over which these preparations were administered and in changes in the hormone introduced by lyophilization. For example, the first preparation which gave such strongly positive effects in the first patient studied in 1948, produced febrile reactions in other laboratories and was ineffective in producing anabolic changes. This preparation was originally supplied to us and other laboratories in the lyophilized form. But, unfortunately, the machines used for its lyophilization were inefficient and were subsequently discarded for more effective ones. We exposed this preparation to a variety of chemical studies and found that it could not be dissolved at a *pH* in which growth hormone should go into solution and there were as well as other evidences of its gross denaturation. We did not use this material but instead had the Armour laboratories send us other lots of the same preparation, not in the lyophilized, but in the frozen state, in which it was kept until use and then thawed prior to its injection. It is quite possible that the excellent anabolic effects achieved with the frozen preparation, in contrast to the catabolic effects obtained in other laboratories, were due to the fact that we used this denaturized preparation instead of the lyophilized one used in other laboratories.

While on the subject of toxic effects and the possible influence of other hormonal contaminants, I want to say a word in appreciation of the splendid way in which the Armour Research Laboratories persisted in their efforts to provide an effective growth hormone preparation in spite of the formidable difficulties which are usually introduced in going from small scale to large scale production. Our own job in carrying out these metabolic studies in the human is, in contrast, rather pedestrian. The Armour Research Laboratories are to be congratulated on the progressive improvement of their preparative techniques which have resulted in the production of increasingly more effective preparations, gratifyingly free of side effects.

Dr. Kinsell has reported that his first successful response to growth hormone was in a hypothyroid patient and suggested that this response may be attributed to the inability of this patient to respond to contamination of the hormonal preparation with thyrotrophic hormone. In contrast, the second patient on whom we reported today failed to show an anabolic response while she was hypothyroid and only did so after we had restored her to euthyroidism by the administration of thyroid hormone. It would seem that our experiences are too limited, at this time, to permit any conclusion as to the relation between the thyroid status of the patient and the capacity to respond to growth hormone preparations. Our first patient who showed such an excellent anabolic response was euthyroid throughout.

Finally, I want to reemphasize the necessity of prolonged administration of growth homone in ascertaining its effects. From inspection of our data, even the subject showing the most striking response to growth hormone had a slightly negative balance during the first week of administration and did not show an anabolic effect until towards the end of the second week; it was most marked in the third week. Had we limited our observations to one week of administration we would have had to conclude that the growth hormone had produced a catabolic rather than an anabolic effect in this patient.

Changes in the Pattern of the Smaller Blood Vessels in the Bulbar Conjunctiva in Children of Diabetic Mothers †

A Preliminary Report

Jorn Ditzel, M.D., Priscilla White, M.D., and Janine Duckers, M.D., Boston

The many advances in the treatment of diabetes mellitus have increased the life span of the diabetic and consequently changed both the clinical picture and the pathological manifestations of the disease. During the last decades widespread vascular degeneration has increased alarmingly in incidence and is now responsible for the vast majority of deaths, even in juvenile diabetics.

The relationship between the metabolic disturbance and the vascular syndrome in diabetes is not known. Although many factors may play a role in the development of vascular changes, there is some evidence that careful regulation may help delay the onset of these in the younger diabetics[1, 2]. This suggests that the vascular degeneration is a consequence of the disturbance of that phase of metabolism that is controlled by insulin.

The possibility exists, however, that both the metabolic change and the vascular lesions reflect a still unknown underlying disturbance. Also the inheritance of a "poor" vascular system gene-linked with diabetes has been suggested as another possibility[3, 4]. The last two suggestions have been given some support by the realization that both morphological and functional changes in the smaller blood vessels may occur early in the diabetic state[5].

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†The term "diabetic mothers" used throughout this paper refers to young mothers in whom the onset of diabetes nearly coincided with or preceded the pregnancy. In the majority of mothers (56) the diabetes preceded the pregnancy.

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Application of the stereoscopic dissecting microscope in the study of the conjunctival vessels in diabetics has lent added emphasis to the importance of capillary and venular changes in the vascular syndrome, particularly in juvenile diabetics[6]. The observation of certain characteristic capillary changes in some young diabetics with only a few weeks of symptomatic disease and in some nondiabetics with an immediate familial history of diabetes suggested that capillary changes may precede the more obvious disturbance in carbohydrate metabolism. Thus it is possible that the capillary changes are indicative of a genetic or early hormonal factor as part of the basic etiology of diabetes.

The above observations stimulated further investigation of the changes in the vascular pattern in the conjunctiva. As part of a large study on individuals with diabetes in their immediate family, an examination of the bulbar conjunctiva was performed. Other aspects surveyed included glucose tolerance tests and growth and development studies. This report presents the results of the conjunctival study in apparently healthy children of diabetic mothers.

MATERIAL

The material consisted of 150 selected children: 75 children of diabetic mothers and 75 children of presumably nondiabetic parents. The children, evenly divided as to sex (37 being males), were grouped into the following age ranges: 0-4 years, 5-9 years and 10-16 years. Each age group contained an equal number of children of diabetic mothers and of controls. All children were apparently healthy. Precaution was taken to rule out local conjunctival irritation, allergy and infections, since these conditions might cause changes in the vascular bed interfering with this study. The children of diabetic mothers studied included 12 who were born from one

to four years before the recognition of diabetes in the mother, 7 whose birth coincided with the onset of maternal diabetes, and 56 who were born subsequent to the recognition of the disease. The duration of the maternal diabetes at the time of the birth of the child varied from 0-21 years (Table 1). The age at onset of

TABLE 1
Duration of maternal diabetes at the time of the birth of the child

Duration in Years	Number of Cases
0-4.9	16
5-9.9	22
10 or more	18

the maternal diabetes varied from 4-36 years. In 17 mothers the onset of diabetes occurred between the ages of 4-15 years, in 23 between the ages of 16-25 years and in 32 mothers after their 25th year. All of the diabetic mothers were receiving insulin. During 48 pregnancies hormones were administered according to the criteria used by White[7]. Of the 75 children, 27 were delivered by the pelvic route and 48 by cesarean section.

METHODS

To avoid as far as possible the subjectivity of the technic employed, it was deemed essential to separate the selection of the subjects and their examination. All conjunctival examinations were carried out by the same observer (Ditzel), and only at the completion of the study were the conjunctival findings compared with the results of the medical history and the glucose tolerance test in the children of diabetic mothers. During the conjunctival examination the subject was placed in a recumbent position and a Leitz stereoscopic microscope (model Knisely, magnifying power 16-150 times) was directed against the bulbar conjunctiva which was illuminated by a Shahan ophthalmic lamp (minimal temperature effect)[8]. The lateral parts of the bulbar conjunctiva of both eyes were examined and a detailed description of the vascular topography and the vascular, extravascular and intravascular status was made immediately afterwards. The study concerns only changes in the extensive superficial network, because this network anatomically and embryologically is related to the vascular system of the subcutaneous tissue in other parts of the body. No evaluation has been done on changes in the pericorneal vessels. The following information about vascular, extravascular and intravascular status was always recorded:

1. Vascular Changes*
   a. Configuration of the arterioles (dilatation, constrictions, color-change along arterial blood stream).
   b. Configuration of the capillaries (localized dilatation, constrictions, microaneurysms, elongation, angular tortuosities and nodularities).
   c. Configuration of the venules (localized dilatation, constrictions and sacculations).
   d. Ratio between the diameter of the arterioles and the accompanying venules.
2. Extravascular Changes
   The presence in the conjunctival tissue of edema, localized or diffuse "hyaline" infiltration†, hemorrhages and pigment from old hemorrhages.
3. Intravascular Changes
   A description of the hemodynamics in different parts of the vascular compartment was made. This included an indication of the degree of aggregation of the blood cells. In certain cases the velocity of blood flow was measured in capillaries and venules by timing with a stopwatch the passage of a mass of red blood cells along the length of the small vessel measured by a calibrated ocular scale.

Registration of the observed changes was made possible with photographic technics.

Glucose tolerance tests were performed on all children of diabetic mothers. The quantity of glucose given depended upon age and body weight. Under the age of 3 years, 3 gm. of glucose per kg. of body weight was given; above the age of 3, the amount was 2 gm. per kg. up to a maximum weight of 50 kg. Thereafter the standard dose was 100 gm. Blood sugar tests were made fasting and at one-half hour, one hour and two hour intervals after the glucose. The blood sugar was determined according to the method of Folin-Wu[9] and Folin[10]. The majority of the determinations were made upon capillary blood. The diagnosis of diabetes was made if the child showed glycosuria and the capillary blood sugar rose to 250 mg. per 100 cc., or the venous blood sugar rose to 170 or above. The condition was indicated as borderline if the fasting capillary blood

*A localized widening of a vessel exceeding its double diameter is called a sacculation; a smaller widening is called a dilatation. A distension is a uniform increase in the diameter of a vessel. A microaneurysm is defined as a globular capillary sacculation with visible afferent and efferent vessels. It must be realized that it usually is impossible to observe the vessel wall itself, and that its configuration must be judged by inference from the outline of the blood stream. Occasionally, in cases with considerable thickening the wall might be seen directly.

†"Hyaline" infiltration is a localized or more diffuse cloudy, structureless, partly avascular area without elevation of the surface of conjunctiva.

sugar exceeded 140 mg. per 100 cc. or the postprandial capillary blood sugar varied from 200 to 240.

RESULTS

Although there were found some individual variations in the vascular and hemodynamic pattern of the bulbar conjunctiva, the configurative and hemodynamic changes observed in the children of diabetic mothers were well-defined and differed markedly from those of the control children. No single feature described was invariably found in the children of diabetic mothers, but the combined vascular and hemodynamic pattern of many of the children appeared similar to those changes reported in juvenile diabetics[6]. Thus even with the first few children examined it was realized that the abnormal pattern might be significant. This supposition was strongly supported later since the entire study revealed that a surprisingly large number of the children of diabetic mothers had abnormal glucose tolerance tests.

NORMAL TOPOGRAPHY OF THE BULBAR CONJUNCTIVAL VESSELS IN CHILDREN

The pattern of the conjunctival vessels is formed by larger arterioles and venules in parallel formation and by capillaries and smaller venules (12-60 micron) in a delicate and rather regular network (Figure 1). The arterioles, which have a straight, even course, show a decreasing diameter, bifurcate giving rise to terminal arterioles. The capillaries arise from the tip of the arterioles forming a moderate anastomosing network which develops a more extensive venular system. Many terminal arterioles can be followed more directly to a venule as a long, unanastomosing channel. The larger venules, which show variable smooth curlings and increasing diameter, are usually situated slightly superficial to the accompanying arteriole. The ratio between the diameter of the arteriole and the venule is relatively constant, being 1:3-1:2.

FIGURE 1. The conjunctival vascular bed of a child (12 years) of nondiabetic parents. The arteriole (A) and the venule (V) are parallel to one another and the capillaries (C) follow a smooth course. Scleral vein (S). (Magn. 72)

CHANGES IN THE BULBAR CONJUNCTIVA IN CHILDREN OF DIABETIC MOTHERS AS COMPARED TO CHILDREN OF NONDIABETIC PARENTS

The vascular pattern in the children of diabetic mothers showed various degrees of irregularity due to changes in all components of the terminal vascular bed, particularly in the capillaries and venules (Figure 2).

FIGURE 2. The conjunctival vascular bed of a nondiabetic child (12 years) of a diabetic mother showing Grade 2 changes. The venules are distended and the ratio between the diameter of the arteriole (A) and the venule (V) is 1:6 or more. The capillaries (C) are prolonged with angular irregular course. (Magn. 72)

VASCULAR CHANGES*

Arterioles: An even and regular course of the arterioles was generally found. The observation of most interest concerning the arterioles was the abolishment of normal parallel formation of the arterioles and larger venules. This feature was observed in 23 per cent of the children of diabetic mothers and never in the control children. The difference is statistically significant ($p<0.01$).

Capillaries: The capillaries were increased in number and formed an extensive anastomosing and irregular network. The most characteristic changes were found in the venous part. This in varying degree showed elongation with angularities and tortuosities. This feature was found in 48 per cent of the children of diabetic mothers and to a much lesser degree and in only 4 per cent of the control children. The difference is statistically significant ($p<0.01$). Accompanying this change were often small irregularities in the configuration of the venous part of the capillaries such as nodularities and focal constrictions. Sometimes, the venous part of a capillary branched and then reunited, so that an ellipsoid ring was formed proximal to the junction of the capillary with the collecting venule. This change was noted in 24 per cent of the children of diabetic mothers and was only seen in a single instance in the control children. Also this difference is significant ($p<0.01$). Smooth or spiral-like hairpin deformations of the direct arterio-venous channel were observed in the children of diabetic mothers. This elongation appeared to be the early stage of the characteristic "corkscrew formation" observed in 10 per cent of young diabetics with long duration of the disease.

Venules: The venules also showed an elongated and irregular course with angularities and loop formations. It is admittedly difficult quantitatively to measure venular elongation, but this change was a characteristic feature in the pattern. It was determined as significant in 45 per cent of the children of diabetic mothers as compared to 7 per cent in the control group. Smaller irregularities along the configuration of the smaller venules were observed in 49 per cent of the children of diabetic mothers compared with 4 per cent in the control children. The differences in incidence of both changes are significant ($p<0.01$).

Associated with the elongation of the venules was a notable distension. This was observed by a change in the ratio between the diameter of the arteriole and the accompanying venule up to approximately 1:6. The venules had a congested appearance and the rate of blood flow was decreased. This distension was found in 43 per cent of the children of diabetic mothers and only in one instance in the control children. The difference is highly significant. The distension was occasionally extended to include the venous part of the capillary (8 per cent). In a single case the venules, besides showing a uniform distension, showed in two places a localized bizarre swelling of the same type as has been seen in the retina[11]. A subsequent glucose tolerance test in this child revealed that it was diabetic.

EXTRAVASCULAR CHANGES

Edema: Microscopic and occasionally macroscopic edema was observed in 15 per cent of the children of diabetic mothers and never noted in the control children.

"Hyaline like" infiltration: Local changes in the extravascular conjunctival tissue, described in the ophthalmological textbooks as hyaline degeneration or hyaline infiltration was observed in 19 per cent of the children of diabetic mothers, but was never observed in any of the control children. It consisted of a partly avascular greyish-white, structureless area in the conjuctiva. It was mostly accompanied by edema of the conjunctiva. It should be emphasized that the term "hyaline" used here does not indicate that this change has been identified as a substance similar to that in the glomerulus in diabetic glomerulosclerosis or that in the retina in diabetic retinopathy.

The incidence of these extravascular changes was significantly higher in the children of diabetic mothers as compared to the control children. ($p<0.01$.)

Hemorrhages: Only in one case was a large punctate hemorrhage seen in the conjunctiva. This child had an abnormal glucose tolerance curve (borderline).

INTRAVASCULAR CHANGES

In the children of diabetic mothers the circulating blood cells were aggregated and formed clumps of various sizes and rigidity. Intravascular aggregation was found in 53 per cent of the children of diabetic mothers. Extensive aggregation of such rigidity and size as to be able to plug terminal arterioles occurred in 3 per cent (Grade 3). Aggregates not visible in the arterioles but present in the capillaries and the venules were found in 25 per cent (Grade 2). Any aggregation of the blood cells of the above degrees had a visible effect in slowing down the rate of blood flow and aggregates occasionally formed "pseudothrombosis" in the capillaries and smaller

* No distinction has been made as to sex and age in the figures quoted since no significant differences were found.

venules. Minimal aggregation, which only was visible in the venules, was found in 25 per cent of the children of diabetic mothers (Grade 1). In the control children, however, minimal aggregation of the blood cells was only found in 4 per cent and never any more extensive aggregation. This difference is highly significant.

GRAPHICAL AND STATISTICAL ANALYSIS OF THE RESULTS

In order to help in the interpretation of the changes, the vascular and extravascular findings were graded according to an arbitrary scale.

Grade 0: The configuration of all vessels was perfectly regular. No elongation of the capillaries or venules was present. No "hyaline" infiltration or hemorrhages were seen.

Grade 1: The configuration of the smaller venules had minor irregularities or a few capillaries showed an angular course. The venules could be elongated. No changes appeared in the conjunctival tissue.

Grade 2: More capillaries showed a characteristic angular course and irregularities. The venules are elongated. The conjunctival tissue may contain edema or "hyaline" infiltration.

Grade 3: Most capillaries showed the above changes. The venules may show in addition to the above mentioned characteristics some other major configurative changes. The conjunctival tissue contained edema, "hyaline" change or hemorrhages.

This arbitrary scale is a revision of a scale previously used in a paper concerning preliminary studies in diabetics[6]. The scale revision is based on greater experience with the study of the conjunctival vessels and was prepared by the observer (Ditzel), with aid of an unbiased individual (Duckers) using a point analysis of the described changes.

The distribution of the vascular and extravascular changes appears in Figure 3. It may be seen that the children of diabetic mothers have much more marked changes than the control children as judged by the arbitrary scale. None of the control children had changes which fell into Grades 2 or 3.

OTHER SIGNIFICANT FINDINGS IN THE CHILDREN OF DIABETIC MOTHERS

The all-inclusive study on the children of diabetic mothers not only revealed conjunctival changes mentioned above, but also a high incidence of diabetes, obvious growth peculiarities such as tall stature, obesity and advanced bone and dental development and elevation of urinary excretion of 17-ketosteroids. Complete

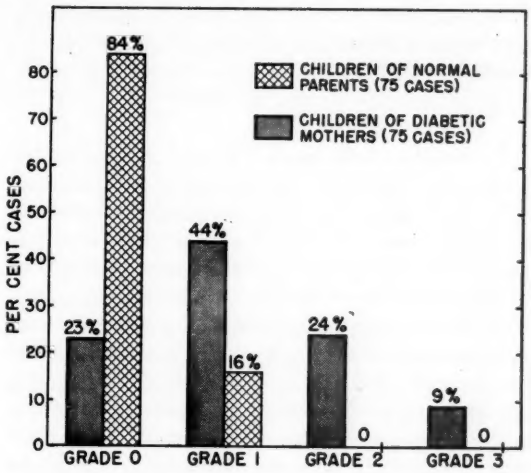

FIGURE 3. Distribution of the degree of vascular and extravascular changes in the conjunctiva of children of diabetic mothers and children of normal parents.

analysis of these results will be the subject of another report. An analysis of the relationship of the conjunctival findings and the results of the glucose tolerance tests and growth studies is given below.

Relationship Between the Vascular Changes and the Result of the Glucose Tolerance Test: The distribution of the vascular and extravascular changes in the bulbar conjunctiva related to the carbohydrate tolerance of the individuals can be observed in Table 2. It can be seen that all cases which had abnormal glucose tolerance tests, diabetic or borderline, showed some vascular changes and all diabetics except one were found to have marked changes of the Grade 2 or 3 types. It can also be seen that all the cases with no vascular changes had normal glucose tolerance tests and none of those with such a normal test had Grade 3 changes.

TABLE 2

The relationship between the vascular changes and the glucose tolerance test performed in the children of diabetic mothers

Classification	Grade 0	Grade 1	Grade 2	Grade 3	Total No. of Cases
Nondiabetic	17	28	10	0	55
Borderline	0	4	5	4	13
Diabetic	0	1	4	2	7

According to the X^2 test there is a significant association between the degree of vascular changes and the decrease in carbohydrate tolerance in children of diabetic mothers ($X^2 = 29{,}61$ $P<0.01$).

Relationship Between the Vascular Changes and the Result of Growth and Development Studies According to Wetzel's Channel[12]: Table 3 indicates a positive correlation between the vascular changes and the degree of deviation of growth in the children according to Wetzel growth channels. Fifty two per cent of 23 children whose growth channel was A_4 or greater had vascular changes of Grade 2 or 3 severity compared with 18 per cent in A_1-M-B_1 channel combined. This difference is 2.5 times the standard error. This positive correlation might become even more obvious, since some of the diabetic children who at the time of examination fell into A_1-M-B_1 channel were obese (A_4 channel) prior to the development of diabetes.

TABLE 3

Relationship between the vascular changes and growth according to the Wetzel grid in children of diabetic mothers

Number of Children	Clinical Rating	Channel	Degree of Vascular Change 0	1	2	3	
23	Obese	A_4->A_4	3	8	9	3	52%
10	Stocky	A_3 - A_2	3	6	1	0	
33	Normal	A_1 - M - B_1	10	17	3	3	18%
9	Slender	B_2 - B_3	1	3	5	0	

There was no demonstrable correlation between the vascular changes and age at onset of maternal diabetes, duration of maternal diabetes, insulin requirement or hormonal treatment during pregnancy and the age of the child examined.

COMMENTS

This study of the smaller blood vessels in the bulbar conjunctiva indicates that certain well-defined differences exist between the combined vascular and hemodynamic pattern in children of diabetic mothers and in children of nondiabetic parents. These differences appeared not only in the children who were found to be diabetic but also in some of the "healthy" children of diabetic mothers. It seems therefore that the pattern change is probably related to factors other than the detectable clinical or chemical diabetes *per se.* Since the observed changes in the smaller blood vessels in children of diabetic mothers have marked similarities to those in normotensive diabetics[6] and since also a large percentage of the children were found to have abnormal glucose tolerance tests (27 per cent), it is suggested that the changes may represent a response which reflects an alteration in the hormonal situation in these children. The consequent metabolic disturbances initiate and may be responsible for the development of vascular changes in these children.*

Our knowledge about the integral function of the capillary bed is meagre, and any causal connection between the demonstrated changes and the development of diabetes is not likely but cannot be excluded. However, the frequent observation of edema and "hyaline" infiltration in the conjunctival tissue of children of diabetic mothers suggests that there is a concomitant alteration of the membrane function of the capillaries. The finding of more marked aggregation of the circulating blood cells implies that there is a decrease of the suspension stability of the blood and a change in the normal protein pattern[13,14]. It may be of interest that Campbell[15] recently has found that highly purified growth hormone greatly decreased the suspension stability of the blood as measured by the erythrocyte sedimentation rate in dogs and that this effect was most manifest when the diabetes induced by the growth hormone was also at a maximum.

Various explanations can be found for the observed changes in the vascular pattern in the children of diabetic mothers. One explanation might be the inheritance of a defective vascular system which may remain at a somewhat immature level. Infants of diabetic mothers tend to be larger than normal. However, there is some evidence that these infants should be regarded as large prematures rather than postmatures. It has been found that in some infants of diabetic mothers, the kidney glomeruli showed immaturity even though the gestational age was about 35 weeks[16]. It is found that in

* Recent studies based on serial observations in young diabetics during and after pregnancy have demonstrated that the venular distension and the capillary changes, particularly in short term cases, are reversible. This strongly supports our suggestion that these vascular changes constitute a response to some transient noxious stimulus common to the metabolic disturbances of the diabetic and the prediabetic. The insult acts locally on the vessel wall (endothelial cell or the basement membrane) most obviously on the venous side of the peripheral vascular bed. (To be published by the authors).

diabetics as well as in their offspring, there is a high occurrence of defects which are mesenchymal in origin as is the vascular system[4].

An endocrine basis for the changes in the vascular pattern is another obvious possibility. The finding of obvious growth peculiarities such as tall stature, obesity, advanced bone and dental development, a high incidence of diabetes and elevated urine 17-ketosteroid excretion in the children of diabetic mothers definitely suggests a hyperactivity of the pituitary in these children. In this study there was found a positive correlation between the degree of vascular change and the abnormality in the glucose tolerance test. This positive correlation was also found between the degree of vascular change and the degree of growth and development as measured by the Wetzel grid. This suggests that all three abnormal findings may be due to the same common underlying disturbance. The large body size in the infants of diabetic mothers has been attributed to overactivity of the maternal pituitary[17]. It has been found experimentally that it is possible to produce giant rat fetuses by the administration of growth hormone to the mother during pregnancy[18]. Injection of anterior pituitary extracts and purified growth hormone can produce permanent diabetes in animals[19,20]. It is generally agreed that hyperfunction of the pituitary brings about an acceleration of vascular degeneration in the larger vessels and that hypopituitarism has the opposite effect[21]. Information concerning the effects of the pituitary hormones on the smaller vessels is extremely limited. However, Becker[22] has recently shown that in rabbits made diabetic with alloxan and injected with corticotropin (ACTH) a marked distortion of the capillary pattern as well as definite microaneurysms was found in the retina.

Thus the underlying disturbances which produce the observed vascular changes, the abnormality in the glucose tolerance test and the abnormality of growth and development in the children may be due to a dysfunction of the pituitary.

Our study strongly supports the concept that there exists a prediabetic state. This is suggested by observation made upon diabetic children at the onset of their disease of (1) increase in height and weight, (2) advance in bone and dental development, (3) elevation of 17-ketosteroid excretion and (4) increase in the level of follicle stimulating hormone (FSH) in serum, as well as (5) vascular changes in the smaller vessels.

Although the material presented is obtained from too small a sample on which to base final conclusions, it is indicative of the presence of early hormonal changes. Furthermore, the implication of this study is that further investigations of children of diabetic mothers may give information concerning the etiology and possible protecting or reversing factors in diabetes.

SUMMARY

A preliminary study of the smaller blood vessels and their hemodynamics in the bulbar conjunctiva of diabetics indicated that even with very short duration of the disease, evidence of capillary changes was present. Since also some subjects with diabetes in their immediate family were found to have similar changes, an investigation was made of the vascular pattern in healthy children of diabetic mothers.

The results of this study showed that many of these children had more marked and different changes in the vascular bed than did the control group of healthy children of nondiabetic parents. The changes in the children of diabetic mothers appeared similar to those of young diabetics. This was of particular interest when it was found in the overall study of these children that they also showed a high incidence of diabetes as shown by glucose tolerance test. In addition, these children showed abnormal growth and development as well as elevated 17-ketosteroid excretion. There was found a positive correlation between the degree of vascular changes in the smaller blood vessels and an abnormal tolerance test as well as to growth peculiarities according to Wetzel's grid.

Therefore, it is suggested that the precipitating factor of these abnormalities is the same and that possibly it may be of pituitary origin.

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DISCUSSION

DR. WILLIAM P. BEETHAM (*Boston*): The blood vessel changes observed clinically in the eyes of patients with diabetes mellitus cannot be minimized. You are all familiar with the marked changes in the retinal veins and venules, the extensive proliferation of capillaries in retinitis proliferans, the small saccular microaneurysms in the retinal capillaries, and the blood vessel proliferation on the iris in an occasional eye with rubeosis iridis. It would not be heresy, therefore, to anticipate changes in the blood vessels of the conjunctiva in the typical diabetic patient. As a matter of fact, the presence of small microaneurysms in the limbal capillaries has already been reported.

Dr. Ditzel has studied the conjunctival vessels with binocular magnification in many patients. The modern slit lamp, or biomicroscope, makes it possible for the ophthalmologist to make similar studies with similar magnifications.

Unfortunately, conjunctival vessels are quite exposed and are subject to many factors and influences such as heat, cold, wind, vitamin deficiency, allergy, infection, heredity, eye strain, and others. Any of these is capable of producing changes in the vascular picture of these vessels which, to some extent, resemble those described by Dr. Ditzel, but which, of course, have no relation to diabetes or general vascular disease. Conjunctival blood vessel patterns have been described in hypertensive vascular disease, and these changes are quite similar in many respects to those which have been described here as pertaining to diabetes.

Dr. Ditzel reports a vascular pattern in the conjunctiva of diabetics and prediabetics. This latter group of patients has no evidence of retinal pathology, hypertension, albuminuria, vessel calcification, and almost no diabetes. The vessel changes in these patients could not therefore be due to sclerosis. What, then, is the nature and explanation of these so-called vessel changes? One is forced to assume that the changes represent some peculiar hereditary vascular pattern, seen in young pre-diabetics or diabetics, or one must, on the contrary, assume that the observations made are less significant and less definitive than our author would have us believe.

Conjunctival vessels have not been adequately studied. Most ophthalmologists—and I include myself—pay little attention to these vessels, and possibly because of this I have found it hard to recognize these vessel changes Dr. Ditzel has described. I do not believe it is possible as yet, with the data presented, to accept fully his conclusion that a characteristic vascular pattern exists in diabetic patients.

Tissue Electrolytes and Water in Diabetic Acidosis

Observations on Alloxan-Diabetic Rats with Ketoacidosis

Harvey C. Knowles, Jr., M.D., and George M. Guest, M.D., Cincinnati*

Diabetic acidosis is accompanied by losses of body water and electrolytes. The numerous investigations designed to define these losses[1-5] have employed mainly technics of metabolic balances which disclose deficits from the body as a whole. Little information concerning the sources of these losses has been published. Guest[6] and Nichols and Nichols[7] have reported a decrease in potassium content in erythrocytes in humans with ketoacidosis. Keitel reported a decreased potassium content in skeletal muscle obtained by biopsy in one human subject[8]. In a preliminary report the present authors have described a decreased content of potassium in muscle in alloxan diabetic rats with ketoacidosis[9]. It is the purpose of the present report to present further observations on tissue water and electrolytes in rats with ketoacidosis, amplifying that preliminary report.

METHODS

Adult white rats of Rockland Farm strain were used, averaging 300 gm. in weight and ranging from 6 to 9 months of age. The animals were kept in glass metabolism cages[10], and fed Purina Chow diet. Three groups of approximately 35 animals each were studied: a control group, and two groups treated with alloxan. In the latter two groups diabetes was induced with alloxan, 50 mg. per kg. injected intravenously after a 24 to 30 hour fast. In one alloxan-treated group (Acidotic I), the animals were fed for 24 hours after receiving alloxan. No insulin was administered. Then food was withheld, and ketoacidosis developed usually in two to four days. In the other alloxan-treated group (Acidotic II) the animals were fed and received NPH insulin daily until constant weight was maintained, usually a period of seven or more days. Then food and insulin were withheld, and ketoacidosis developed within two to four days. The waiting period introduced for Group II was to allow immediate toxic effects of alloxan, if any, to wear off before the development of acidosis.

Water was available in the cage throughout all experiments. When sacrificed, all animals were anesthetized with nembutal injected intraperitoneally. Blood was drawn from the inferior vena cava and placed in heparinized vials. The thigh muscles were stripped off and dissected as free from fat and connective tissue as possible. The liver was removed and the gall bladder discarded. The heart was removed and the auricles dissected away, leaving ventricular muscle for analysis. All tissues were quickly blotted free of gross blood and transferred to tared bottles.

To determine the water content of muscle, liver, and heart, the tissues were finely minced and then dried at 105 degrees C. for 72 hours, when constant weight was attained. To determine the water content of whole blood and serum, it was found necessary to dry 1 cc. aliquots at 105 degrees C. for 24 hours only. Dried muscle, liver and heart were ground to a homogeneous powder, and fat was extracted, first with ethyl ether and then with petroleum ether in a Soxhlet reflux apparatus. With each solvent constant weight was attained in four hours. Preliminary experiments using other fat solvents showed that although alcohol gave an apparently higher yield of lipids, there were removed also approximately 10 per cent of nitrogen, 20 per cent of sodium and potassium, and 80 per cent of chloride content from heart, liver, and muscle. Consequently, although alcohol may extract more lipids than ether, the calculated per cent fat content may be erroneously high. Furthermore, as ether removed no nitrogen or minerals, it was not necessary to return the extract to

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the original dry tissue. Following the extraction, aliquots of the fat free powder were ashed in a muffle oven at 500 degrees C. overnight in silica crucibles. One cc. of warm 1.0 N HCl was added to the ash in each crucible and the contents were diluted for determinations of sodium and potassium by flame photometry.

For determination of tissue chlorides, the method of Eichelberger and Bibler was found most satisfactory[11]. Several other methods were investigated including those of Harrison and Darrow[12], Lowry and Hastings[13], Sunderman and Williams[14], Van Slyke[15], and Heilbrunn and Hamilton[16]. Of these, the methods of Eichelberger and Bibler, and of Heilbrunn and Hamilton, gave equally the largest yield and the most consistent results.

Determinations of sodium and potassium in whole blood were made by flame photometry directly on 1.0 cc. samples hemolyzed with water. Results by this method agreed with those obtained by wet or dry ashing.

Plasma *p*H was determined by the method of Hastings and Sendroy[17], carbon dioxide content by that of Van Slyke and Neill[18], chloride by that of Van Slyke[15], and ketones by that of Guest and Lestradet[19]. Blood hematocrit was determined by the method of Guest and Siler[20], and sugar by that of Nelson[21]. Nitrogen was determined on dry fat-free tissue aliquots by the microkjeldahl method.

Calculations of the extra and intracellular spaces in muscle were done by the method of Yannet and Darrow[22].

All tissue samples were ashed in duplicate for analysis. Among the duplicate values so obtained the average deviations from the mean were: for N$\pm$0.67 per cent; Cl$\pm$2.5 per cent; Na$\pm$2.19 per cent and K$\pm$2.2 per cent. Differences between experimental groups were considered significant if the p values were less than 0.02.

RESULTS

In Table 1 are listed data on whole blood and plasma in the control and acidotic animals. The elevations of the plasma ketones and blood sugar, and the depressions of the plasma *p*H and carbon dioxide content in the acidotic groups, are comparable to those found in severe human diabetic ketoacidosis. The rise in hematocrit was less than expected, possibly due to hemolytic action of alloxan. The slightly elevated blood sugar in the control group may be explained by the fact that the samples were taken postprandially, following a previous fast.

In Table 2 are given the findings in muscle, liver, and heart in the normal and ketoacidotic rats. In muscle, expressed per 100 gm. of fat-free solids, in both acidotic groups there were decreases in water and potassium content without significant changes in sodium and chloride content. There was a slight but significant rise in nitrogen content, which might be explained by a relative decrease of minerals and glycogen. The fat content was higher than normal in the group allowed to develop acidosis immediately after receiving alloxan, and lower than normal in the acidotic group of rats maintained a short time first on insulin.

In liver, water and sodium content increased, while there were no significant changes in chloride and potassium content. The fat content increased considerably in both acidotic groups, especially in the group not treated with insulin. Nitrogen in liver increased slightly but significantly, as in muscle, perhaps also due to a relative decrease of glycogen. In heart muscle the water content decreased slightly. There were decreases in both sodium and chloride content, but no significant changes of potassium or nitrogen.

The changes in erythrocyte composition are given in Table 3. In the acidotic groups there was a decrease in water and potassium content with no significant change in sodium content.

TABLE 1

Whole blood and plasma changes in ketoacidosis

Group	Blood			Plasma					
	Hematocrit %	Sugar mg. %	*p*H	Carbon dioxide mM/L	Chloride mM/L	Sodium mM/L	Potassium mM/L	Acetone mg. %	Water %
Control	42.4	121	7.45	28.4	102	142	4.32		93.1
	1.8	15	0.04	2.2	5.2	4.4	0.4		0.3
Acidotic 1	45.3	686	7.08	9.49	91	133	5.52	174	91.2
	4.6	126	0.10	2.9	11.9	10.5	2.0	73	0.6
Acidotic 2	45.5	746	6.99	8.84	90	130	5.93	211	91.2
	5.8	199	0.06	2.0	12.3	11.1	1.6	98	1.1

Mean of 12 determinatives with S. D.

TABLE 2
Tissue composition in ketoacidosis

Group	No.	Fat % of total solids	Per 100 gm. fat free solids: Water gm.	Nitrogen gm.	Chloride mM	Sodium mM	Potassium mM
			MUSCLE				
Control	12	7.0 1.12	308.4 4.4	14.77 .56	5.10 .57	8.22 .65	45.0 1.84
Acidotic 1	12	10.0 2.48	272.8 15.0	15.16 .25	5.25 1.06	8.26 1.43	38.23 2.44
Acidotic 2	12	5.5 1.52	271.4 5.9	15.34 .68	5.23 1.43	8.87 1.01	39.69 2.51
			LIVER				
Control	12	7.34 1.84	265.3 27.9	11.94 .74	10.34 2.91	8.78 1.24	32.9 3.25
Acidotic 1	12	38.9 16.0	330.4 33.4	13.62 .37	11.71 3.82	11.41 1.73	32.0 4.55
Acidotic 2	12	20.7 10.9	310.8 21.7	13.50 .36	11.18 1.57	11.26 1.47	34.4 2.62
			HEART				
Control	9	5.11 0.66	365 15	13.8 0.2	11.3 2.6	16.3 2.4	34.6 2.2
Acidotic 1	9	11.3 1.1	352 9.5	13.9 0.8	7.84 2.8	11.6 1.4	35.7 2.9
Acidotic 2	9	10.4 2.0	348 8.4	13.7 0.3	9.60 1.0	11.2 2.2	35.8 3.8

Mean of values with S. D.

TABLE 3
Changes in erythrocyte composition in ketoacidosis

Group	Sodium mEq/L	Potassium mEq/L	Water gm%
Control	9.66 7.2	109 4.1	66.5 0.78
Acidotic 1	15.0 9.7	89.5 6.1	65.8 1.8
Acidotic 2	7.99 6.0	95.5 9.6	64.8 1.2

Mean of 12 determinations with S. D.

TABLE 4
Derived phase values in ketoacidosis

Group	No.	Per 100 Gm. Fat Free Solids: Extracellular water ml.	Intracellular water ml.	Per liter of Intracellular Water: Intracellular Sodium mEq	Intracellular Potassium mEq
Control	5	42.4	291	9.47	160
Acidotic 1	9	40.0	234	12.9	168
Acidotic 2	8	38.2	236	12.5	165

Derived values for extra and intracellular spaces in muscle and for intracellular concentrations of sodium and potassium are listed in Table 4. The greater part of the water loss appeared to be intracellular with little change in the extracellular space. The concentrations of intracellular sodium and potassium, expressed per liter of intracellular water, increased slightly but not significantly.

COMMENTS

Except for alterations in fat content there were no significant differences between tissues of the two acidotic groups. Since the degree and duration of ketosis were the same in both groups, it would appear that the period of waiting (seven days) for immediate toxic effects of alloxan to wear off did not affect the final results.

The average decrease of water content of muscle amounted to 12 per cent. If muscle mass is assumed to be 40 per cent of the body weight, a parallel loss in a 70 kg. human would amount to nearly three liters. Thus, a major part of the total water deficit in diabetic acidosis appears to be in muscle tissue. The water losses in erythrocytes and heart were relatively less, averaging 7 and 5 per cent respectively. The 17 per cent gain in water content in the liver was unexpected. Recently it has been suggested that factors other than

osmosis are involved in the transport of water across cell membranes[23]. The irregularity of water changes in the tissues studied in this experiment might support this hypothesis. However, if one takes into account the changes in the sums of the sodium plus potassium ions which because of their large concentrations would be most active osmotically, these changes vary grossly with total tissue water content. Furthermore, if the concept of the chloride space is valid, even in severe acidosis, the possible slight increase found in intracellular tonicity in muscle as measured by the sum of sodium plus potassium would be balanced by the high sugar content of the extracellular space. Consequently, from these experiments it cannot be concluded that in the tissues studied there was gross movement of water not corresponding to osmotic activity.

Although few calculations were made relative to extra and intracellular spaces, it is apparent that loss of water was predominately intracellular, at least in muscle, and that the extracellular space decreased slightly if at all. This finding coincides with previous studies by Sunderman[24], but is at variance with balance studies wherein negative chloride balances have been interpreted to mean that water losses were predominately extracellular. This discrepancy might be explained by one or both of two possibilities. First, the extracellular space in muscle may not be in complete equilibrium with that of the remainder of the body. Second, the chloride (and sodium) losses observed early in the course of diabetic acidosis may come from other reservoirs such as bone, and depletion of extracellular sodium and chloride may occur only at a later stage of dehydration with shrinkage of the extracellular space. In the present experiments longer duration of ketosis might have resulted in further dehydration with decrease of the extracellular space. Nevertheless, the intracellular loss was considerable.

The decrease in potassium content of muscle was significant. If these losses are extrapolated to correspond to a 70 kg. human, they approximate those found by the balance studies previously mentioned. Muscle apparently constitutes the main labile reservoir of potassium. These findings correspond with the recent studies of Schwartz and co-workers who showed that in rats made deficient by diet, the muscle loss could account for the entire body loss[25]. There was no replacement of potassium loss by sodium in muscle. This finding may be explained by the short duration of the experiment and by the presence of dehydration.

The absence of change in potassium content of the liver conforms with observations by other investigators wherein states of potassium deficiency induced by diet were not attended by changes in liver potassium[26–28]. The absence of change of potassium content in the heart was unexpected. It is to be noted, however, that in clinical experience cardiac irregularities due to potassium deficiency are unusual prior to therapy and are usually prone to develop when there is rapid restoration of normal carbohydrate metabolism without the administration of potassium. Perhaps when muscle concentration of potassium is below a critical level, and the supply of potassium available is insufficient for glycogen formation, potassium may be momentarily withdrawn from vital areas, leading to transient cardiac irregularities and peripheral neuropareses.

The absence of change in sodium content of muscle is interesting, inasmuch as a lowered content was expected. Why muscle retained its sodium content and the heart showed a decrease in sodium is not clear. The sodium diuresis found early in the course of ketoacidosis[1] may represent sodium released from bone by acidosis[29].

The finding of an increased sodium content of the liver may be related to the gain in water. As there was no significant change in chloride content, it might be postulated that acetoacetate made up the anion deficit. Conceivably, with the massive production of acetoacetic acid, a cation exchange system of sodium and hydrogen could exist at the cell membrane with accumulation of sodium acetoacetate and water inside the cell and carbonic acid formation outside the cell with subsequent liberation of carbon dioxide.

SUMMARY

Studies done on alloxan diabetic rats with severe ketoacidosis, induced by withholding food and insulin, yielded the following findings:

1. Water was lost disproportionately in muscle, heart, and erythrocytes and was gained in liver. A major part of the total body loss of water appeared to come from muscle and was predominately intracellular.

2. Changes in sodium content of the tissues studied (erythrocytes, liver, heart, and skeletal muscle) were not sufficient to account for gross deficits of sodium that are demonstrable by metabolic balance studies. It seems likely that during the development of acidosis, sodium first leaves other reservoirs—perhaps bone.

3. Skeletal muscle appears to constitute the main reservoir of labile potassium. Deficits of potassium in vital organs such as heart and liver may occur only

when the concentration in skeletal muscle has decreased below a critical level.

4. In general, tonicity of body fluids as measured by sodium and potassium concentration was maintained constant.

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DISCUSSION

THOMAS HODGE MCGAVACK, M.D., (*New York*): Several years ago, we performed two-hourly serum and urinary analyses for sodium, potassium and chloride, and, in some instances, phosphate and calcium and urinary determinations for 17-ketosteroids in acidotic patients with diabetes mellitus. Simultaneously cardiographic tracings were made. It was our original intent to establish some quantitative relationship between the values for electrolytes and the alterations in the cardiograms in such fashion that either one or the other might serve as a satisfactory guide for water and elec-

trolyte therapy. We failed in this venture. Furthermore, we did not observe usually described alterations in the electrocardiogram which are expected to accompany hypopotassemia on the one hand or hyperpotassemia on the other.

Changes in the T-waves of the electrocardiogram were usually present in either hypo- or hyperpotassemia, but they could in no way be related quantitatively to the clinical condition of the patient or to the serum content of electrolytes. Figures for serum potassium as high as 12.1 mEq./L. were seen in untreated coma, and as low as 1.1 mEq./L. in subjects from whom potassium therapy was temporarily withheld. In fact, these extremes of values were demonstrated in a single patient. in this instance, no irregularity of cardiac action appeared and the heart block described by others when values for serum potassium reach 2.5 mEq./L. did not occur.

At the time the above-mentioned work was done, we attributed this lack of correlation between the electrocardiograms and electrolyte patterns to the fact that the electrocardiogram reflects not changes in potassium alone but the totality of the effects of the ionic environment. For example, lowering of serum and tissue sodium decreases the hyperkalemic effect. Dr. Knowles' data have indicated a lowering of sodium in cardiac musculature. We were well aware of the fact that serum potassium did not necessarily affect figures for the tissue cells, but quite ignorant of the fact that the heart muscle might maintain normal or "near-normal" values for potassium in diabetic acidosis in the face of severe depletion in other tissues—a fact which Dr. Knowles' presentation seems to demonstrate clearly.

Our own experiments just presented indicate that the need for potassium can not be derived from an interpretation of the electrocardiographic tracings. Further evidence of a similar nature resulted from complementary experiments Dr. Joseph Gast and I did several years ago.

We were intrigued by the rather dramatic changes in cardiac size which attended the use of desoxycorticosterone acetate (DCA) in Addison's disease. In order to study this phenomenon further, intoxicating doses of DCA were given to intact rats. Cardiac roentgenographic silhouettes were measured. When increases of from 30 to 50 per cent in cardiac volume were attained, the animals were sacrificed and cardiac water, sodium, potassium and chloride were determined. Along with increase in water in such hearts, we found both absolute and relative increase in sodium and chloride but the expected decrease in potassium was minimal and not statistically significant.

When coupled with the work just now presented by Dr. Knowles, it seems to us that the results of these experiments indicate a very specific regulatory mechanism within cardiac musculature (and nerves?) which jealously guards the potassium values for that particular tissue and which is destroyed only when the animal (or human being) is in a highly critical condition.

We must then agree that neither the serum potassium nor the electrocardiogram is a wholly satisfactory guide to the administration of electrolytes in the treatment of diabetic acidosis. Clinical findings are still extremely useful. Furthermore, some preliminary studies indicate that the urinary excretion rate and/or concentration will perhaps be our best laboratory criteria of the future for determining the type and amount of electrolyte to be given to the patient in diabetic coma.

The tenacity with which the heart muscle retains potassium, despite cellular depletion elsewhere, is the first dramatic point in Drs. Knowles' and Guest's paper. The second point which invites discussion is the increase in water and sodium found in the liver during severe diabetic acidosis, despite severe losses of both of these materials from other parts of the body. Two explanations come to mind: (1) It is well known that sodium and water are concentrated in areas of trauma. After major surgery, Winfield, Mersheimer and Fox of our institution have observed a fourfold increase in sodium in the skeletal muscle "handled" during the operative procedure, and a simultaneous excessive (two to threefold) loss of potassium in the same area. It seems doubtful that the liver in diabetic coma can be looked upon as a focus of such traumatic nature, as the potassium values are surprisingly well maintained. (2) Our second explanation, and the one we prefer, is related to the excessive formation of ketones. The regulation of fat mobilization and degradation is apparently under the influence of the liver. In diabetic acidosis, the marked acceleration of these processes may set up extremely high values within the liver, which will favor the retention of both water and electrolyte.

In conclusion, it seems to us that the data presented by Drs. Knowles and Guest are in consonance with the concept that the quantitatively estimated need for water and electrolytes in the treatment of diabetic acidosis can be best gauged by clinical findings and by the determination of urinary volume and the urinary concentrations of sodium, potassium, chloride and possibly phosphate.

Effect of Vegetable Fat on Hypercholesterolemia and Hyperphospholipidemia

Observations on Diabetic and Nondiabetic Subjects Given Diets High in Vegetable Fat and Protein

Laurance W. Kinsell, M.D., George D. Michaels, Ph.D., Gilbert C. Cochrane, M.D., John W. Partridge, M.D., John P. Jahn, M.D., and Harry E. Balch, M.D., with the technical assistance of Sadie Smyrl, Marjorie Coelho, Florence Olson, George Fukayama, and S. Rattliff

As previously reported, the administration of formula diets containing large amounts of vegetable fat to nondiabetic patients, with or without elevation in serum lipids, results in a major decrease in the level of cholesterol and phospholipids in the plasma[1]. This statement applies to patients with such diverse conditions as simple obesity, nephrosis, myxedema, hyperthyroidism, rheumatoid arthritis, retinitis pigmentosa, etc. In the present paper will be described the findings in diabetic patients, and in one patient with familial hypercholesterolemia, maintained on formula and non-formula diets containing large amounts of fat which, as indicated in specific instances, is of vegetable, of animal, or of mixed origin.

METHODS

The chemical methods have been described previously[1, 2] as have also the preparation of the formula diets used[3]. The mixed diets containing large amounts of vegetable fat have included considerable quantities of nuts† as a source of such fat, and also as a source of a significant portion of the dietary protein. The initial "vegetable lipid diet" consisted of the addition of nuts in an amount equivalent to 800 calories, to an 800 calorie, high protein, reducing diet. More recently, a variety of nut dishes have been devised which permit of the preparation of a variety of palatable "vegetable lipid diets," in a calorie range from 1500 to 2700, as shown in Table 1.

TABLE 1
Standard diabetic diets

Diet Number	Approximate Calories	Carbohydrate Gm.	Protein Gm.	Fat Gm.	Daily Calories
1	1500	135	98	66	1526
2	1800	118	108	101	1813
3	2100	135	119	123	2123
4	2400	143	132	143	2387
5	2700	160	150	163	2707

OBSERVATIONS

Formula, High Fat Diets in Diabetic Patients

Fourteen diabetic patients have been maintained on such diets in the course of extended metabolic studies. Two of these patients (DID and GAR), on a routine

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Grateful acknowledgment is made to the Armour Laboratories, Associated Concentrates, and Atlas Powder Company for supplies of lipid materials used in these studies.

Address communications to Dr. Kinsell at the above address.

†A portion of the nuts used in this study has been supplied through the kindness of Mr. Jenanyan of Circus Foods, Incorporated.

diabetic maintenance program (see Table 1), had hypercholesterolemia and hyperphospholipidemia. In both patients, the administration of formula diets, containing large amounts of vegetable fat together with relatively large amounts of protein, resulted in a rapid and maintained fall in the levels of serum cholesterol and phospholipids. In patient GAR, the resumption of an average diabetic diet resulted in a prompt return of the serum lipids toward their previous levels (Figures 1 and 2). This increase in serum lipids was associated with a marked worsening of vision, which up to that time had been steadily improving. This may or may not have been coincidental.

Patient EDM, a boy of eighteen with diabetes of considerable severity (insulin requirement on an average diet in excess of 70 units daily), but with no clinical evidence of vascular disease, during a period of twenty days on a formula diet containing 176 gm. of vegetable fat had a progressive fall in serum total cholesterol from 220 mg. per 100 cc. to 107 mg. per 100 cc., and

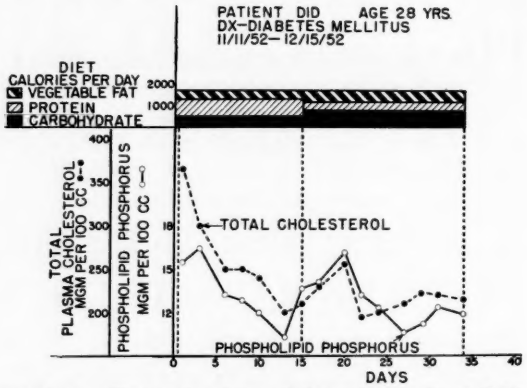

FIGURE 2. Changes in plasma cholesterol and phospholipids in a severe juvenile diabetic during the intake of a diet relatively high in vegetable fat. Previously he had been maintained on a "diabetic No. 2" diet, containing 101 gm. of animal fat. On this "animal fat diet," his cholesterol varied between 350 and 450 mg. per 100 cc. Despite chemically constant hourly feeding throughout the 24 hours and constant insulin, his diabetes was never under optimal control. Courtesy "J. Clin. Nutrition."

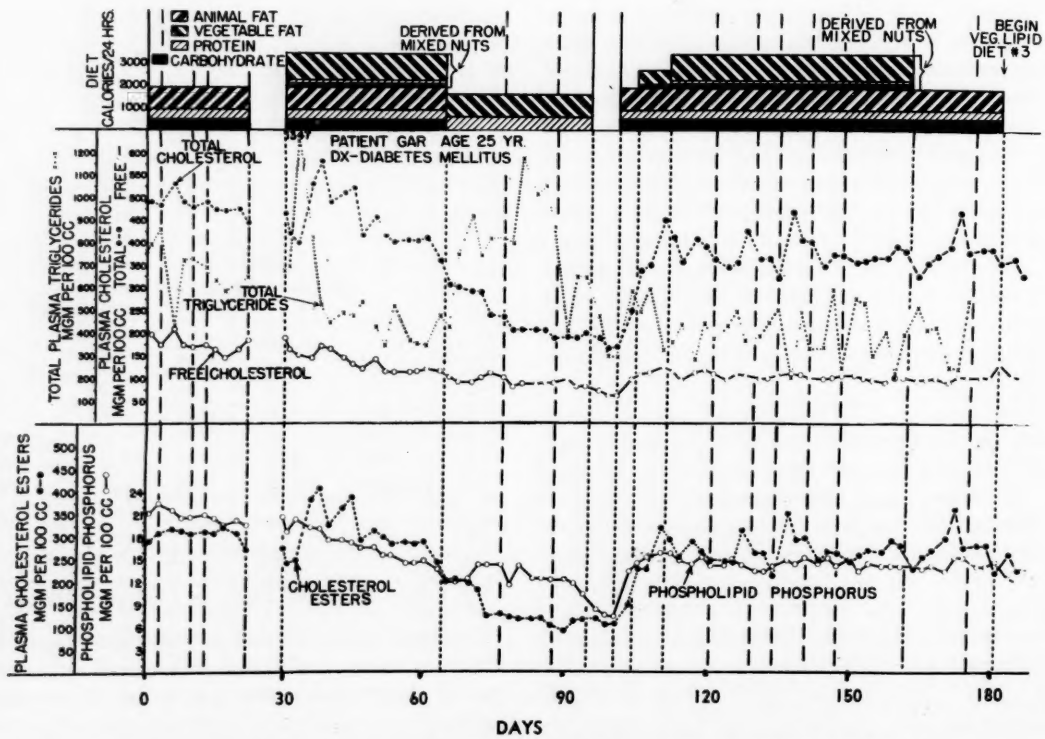

FIGURE 1. The addition of 134 gm. of vegetable fat, derived from nuts, to a high animal fat diet, was associated with a significant fall in serum lipids. The administration of a high vegetable fat formula resulted in a fall to completely normal levels. Despite hourly chemically constant feeding during this period of study, the diabetes was never under optimal control. Courtesy "J. Clin. Nutrition."

of phospholipid phosphorus from 14.75 to 7.25 mg. per 100 cc. (Figure 3).

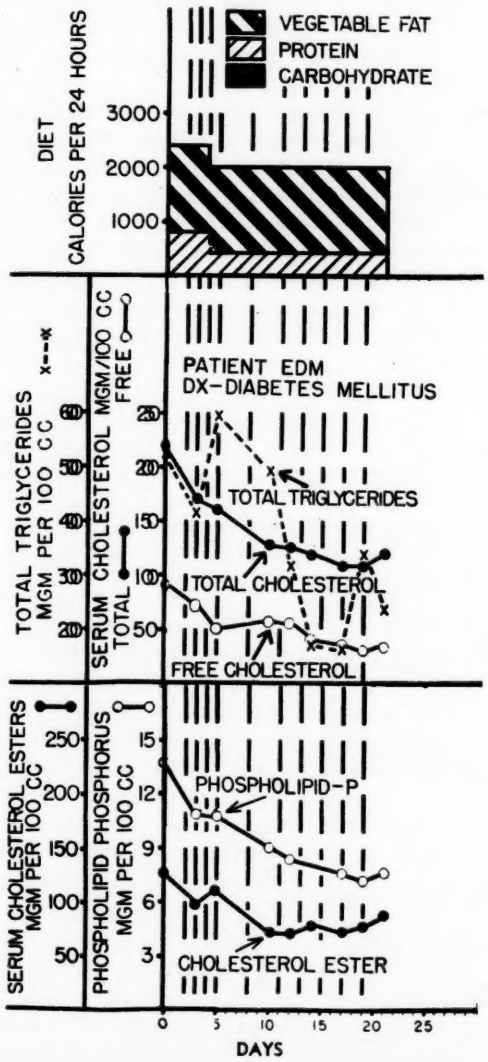

FIGURE 3. Fall in plasma cholesterol and phospholipid during the intake of a high vegetable fat formula in a severe juvenile diabetic.

Effect of Mixed Diets, High in Vegetable Fat, and Containing Little or No Animal Fat, in Diabetics and in a Patient with Familial Hypercholesterolemia

As reported in part elsewhere[4], five patients with diabetes of moderate or marked severity, all of whom had previously been maintained on diets containing relatively large amounts of animal fat and protein, after suitable "base-line observations" of plasma lipids had been obtained, were placed on diets containing amounts of protein, fat and carbohydrate, identical with their previous diets, the fat and a portion of the protein being entirely or almost entirely of vegetable origin. The findings in these patients, all of whom had been selected because they had significantly elevated or high normal cholesterol and phospholipid values, are shown in Figure 4. All of these patients experienced a significant fall in the plasma lipids, in some instances of major magnitude, during the intake of the high vegetable lipid diet. Resumption of the original diet by some of these patients resulted in a prompt return to elevated plasma lipid levels.

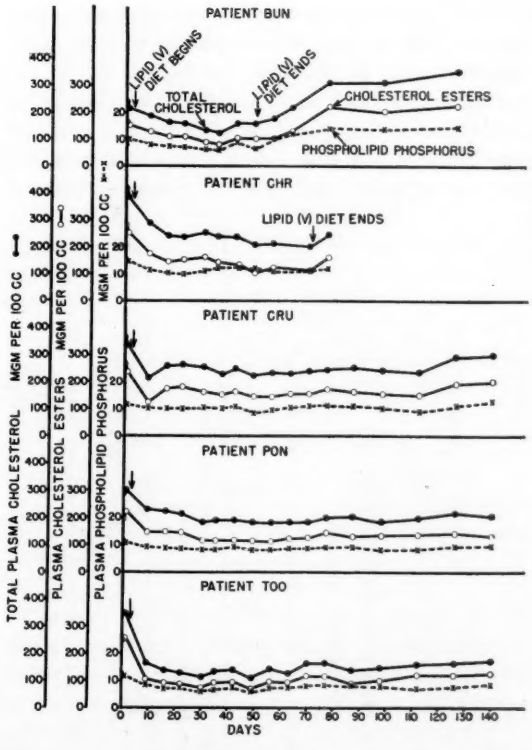

FIGURE 4. Changes in plasma lipids in five diabetics. Patient CRU did not adhere strictly to the vegetable lipid diet after the second or third week.

A patient with "idiopathic hypercholesterolemia" whose plasma lipids had been followed during the intake of an average diet, was placed on the high vegetable lipid, mixed diet, and later returned to an average

diet. The findings are shown in Figure 5. In this patient, and in all of the above patients, the diets administered were fully adequate in a nutritional sense, i.e., they were not associated with weight loss and were associated with at least an equal degree of well being as compared to that experienced on an average diet.

It appeared then that in diabetics, as in nondiabetics, the ingestion of diets containing large amounts of vegetable fat resulted in a predictable fall in the level of serum cholesterol and phospholipids. The question arose as to the reasons for this effect. One might postulate that the change was related primarily to the *absence* of cholesterol in the vegetable fat. (This would not appear to apply in the case of phospholipids, inasmuch as the phospholipid content of the nuts used in the mixed vegetable lipid diets averaged more than 750 mg. per 100 gm. of nuts.) Another explanation would be that vegetable lipids contain sterols or other elements which exert some significant effect upon cholesterol and phospholipid metabolism. It is also thoroughly possible that some other dietary entity or combination of dietary entities in the formula or mixed vegetable lipid diet is in a measure responsible for the effect upon plasma cholesterol and phospholipids.

In an effort to explore further the possibilities, a variety of derivatives of vegetable lipids have been administered to patients in conjunction with high cholesterol diets. Among these agents have been crude "soy-bean sterols"; a mixture of soy-bean lecithin and cephalins; more highly purified soy-bean sterols; and most recently, dihydrocholesterol.

Such a study, under controlled metabolic ward conditions, is shown in Figure 6. The patient, GLI, 52-year-old male with mild diabetes and advanced vascular disease, received in sequence: crude "soy sterols," lot No. 1, emulsified with "Tween 80"*; "Tween 80" alone; crude "soy sterols," lot No. 1, without "Tween 80"; more highly purified soy sterols, lot No. 2, without "Tween 80." Each of the above was administered in conjunction with a "standard diabetic No. 2 diet" (see Table 1).

He was then placed on a chemically constant formula diet containing 120 gm. of vegetable or animal fat respectively (as indicated in Figure 6). During the course of the animal fat formula, he received in se-

*Polyoxyethylene (20) sorbitan monooleate, manufactured and sold by Atlas Powder Company under the trade mark of "Tween 80."

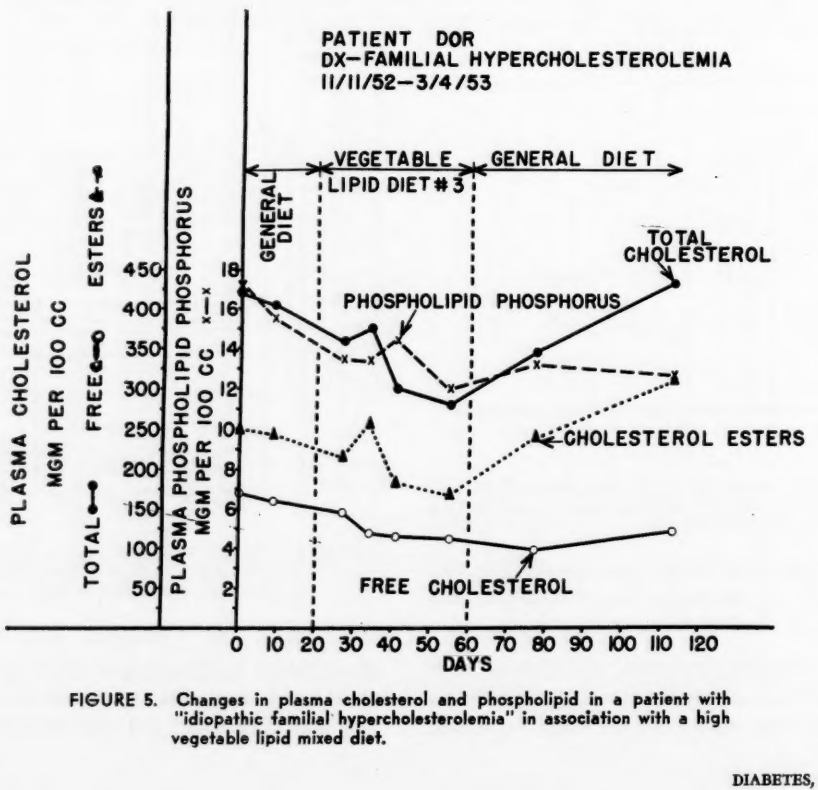

FIGURE 5. Changes in plasma cholesterol and phospholipid in a patient with "idiopathic familial hypercholesterolemia" in association with a high vegetable lipid mixed diet.

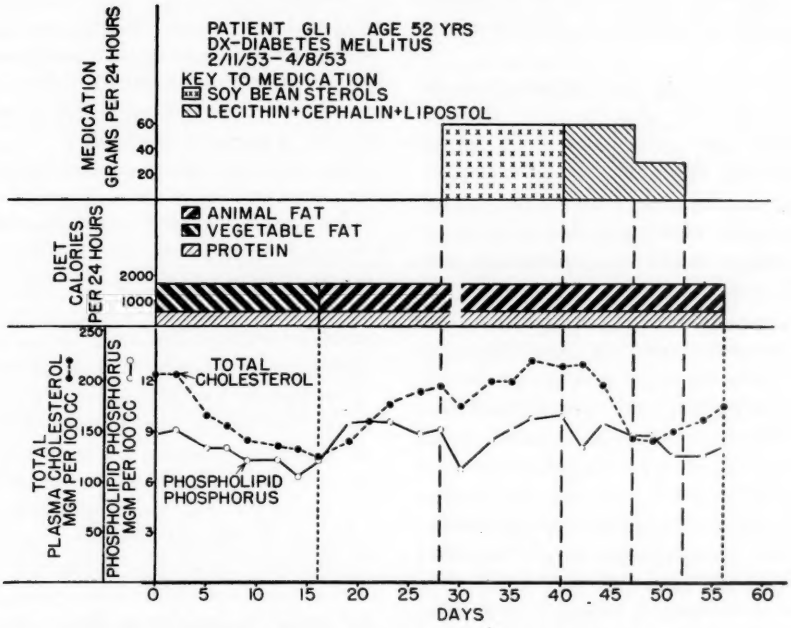

FIGURE 6. Changes in plasma lipids during the administration of soy-bean sterols and soy phosphatides in a middle-aged diabetic with extensive vascular involvement.

quence: soy sterols, lot No. 2; and a lecithin-cephalin mixture derived from soy. The findings are compatible with the interpretation that:

1. The crude soy sterols produced a significant fall in plasma cholesterol which was not dependent upon the presence of "Tween 80." The more highly purified soy sterols produced little or no effect.

2. Intake of a soy lecithin-cephalin mixture was associated with a fall in cholesterol of a magnitude comparable with that occurring during the intake of the crude "soy sterols."

The usual fall in plasma lipids occurred during the intake of the vegetable fat formula.

The foregoing findings suggest that under these conditions some component of a crude soy lecithin-cephalin mixture results in a fall in plasma cholesterol and phospholipids.

If one refers to Figure 1, however, it will be noted that no depression in plasma lipids occurred in juvenile diabetic patient GAR under the conditions of use.

Further studies with lecithin-cephalin mixtures are under way. Also being investigated are compounds which allegedly inhibit intestinal absorption of cholesterol. The administration of 20 gm. of dihydrocholesterol daily to a young severe diabetic, DID, was associated with a fall in plasma cholesterol from 251 to 211 mg. per 100 cc.

COMMENTS

The foregoing studies, and others currently under way, have a two-fold objective—first, to evaluate some of the hormonal and other metabolic abnormalities in diabetic patients; second, to evaluate the effects of diet and of other agents upon the serum lipids in diabetic patients, and if possible to determine whether any correlation exists between serum lipid changes and the progress of existing vascular disease. Only the second problem is considered in this paper.

There is abundant evidence that vascular disease manifests itself at an earlier age period and progresses more rapidly in the diabetic population than in the general population. The reasons for this are by no means clear. Among the possibilities are the following:

1. Recurrent hyperglycemia per se aids and abets in the production of damage to the intima.

2. Abnormal metabolism of lipids results from abnormal energy metabolism, with resultant increase in circulating lipids and increased deposition of lipids in the intima.

If either or both of items one and two are correct,

optimal dietary-insulin control would be of obvious importance from the standpoint of prophylaxis of vascular damage.

3. Abnormal protein metabolism resulting from abnormal energy metabolism and/or from abnormal "hormonal balance" (see below) results in intimal damage with secondary deposition of lipid materials.

4. The production of excessive amounts of adrenal cortical and/or pituitary diabetogenic factors causes abnormalities of protein and/or lipid metabolism with resultant vascular damage.

Whatever the pathogenic factors may be, it has seemed to us that evaluation of as many aspects of lipid and protein metabolism as possible, in the diabetic, should aid in clarifying this very confused field.

As previously described[1], the original observation that in the nondiabetic, diets high in vegetable fat were associated with a fall in serum lipids, was incidental to other studies. The further evaluation of this relationship in the diabetic has been purposeful. In our experience to date, all diabetics maintained on the formula diets, and all but one on the mixed "vegetable lipid" diet, have had profound diminution in the level of their plasma lipids. Young diabetics with extensive vascular disease and hypercholesterolemia appear to be more resistant, that is, a greater period of time may elapse from institution of the diet until the lipids have fallen to normal than in middle-aged diabetics, or than in juvenile diabetics without extensive vascular disease. This observation might suggest the mobilization of depots of endogenous lipids during the early part of the dietary program. (We are aware that this may be a somewhat naïve explanation.)

The reason for the decrease in plasma lipids is as yet not fully apparent. Since the same change occurs in nondiabetics, modification of the diabetic state per se would not appear to provide a suitable explanation. Further, there is little obvious change in the diabetic state in terms of insulin requirement in most patients thus far studied; and the relative stability of the diabetic state per se seems to bear no relationship to the diet-induced changes in serum lipids.

The observation that some lipid material, apparently present in the "crude phosphatide fraction" derived from soy-bean, may cause a fall in serum lipids, at least in some patients, suggests that the effect is an active rather than a passive one. This concept is further supported by the fall in plasma lipids which may occur when large amounts of nuts are added to a high animal fat (high cholesterol) diet.

Peterson's observation with "crude soy-bean sterols"[5] suggested to Siperstein, Nichols, and Chaikoff[6] that dihydrocholesterol might inhibit the absorption of cholesterol. This apparently occurred in their experimental animals. Whether this can be duplicated consistently in humans is still to be determined.

Our own observation in one patient at least calls for further studies of the same kind.

No sweeping clinical implications should be drawn from our findings thus far. Despite a voluminous literature, it is yet to be proven that the level of any serum lipid constituent per se is either of necessity correlated with or responsible for any form of vascular disease in the diabetic or nondiabetic. This statement is documented nicely in a recent paper by Wilkinson et al[7]. Our findings do, however, demonstrate beyond any reasonable question that fat per se does *not* result in increased serum cholesterol levels[1c]; that quite the contrary is the case when diets containing large amounts of vegetable fat are ingested. Further, the observation of significant improvement in vision in two severe diabetics, with advanced retinal pathology during the period of diet-induced fall in serum lipids, would suggest that at least no deleterious effect upon this form of vascular disease results from such a dietary program.

SUMMARY

Administration of diets containing large amounts of vegetable fat to diabetic patients, with or without hypercholesterolemia and hyperphospholipidemia, consistently results in a fall in these lipids. A prompt rise occurs when isocaloric amounts of animal fat are substituted. The evidence available to date suggests that this, at least in part, may represent a positive effect of some lipid material, possibly phosphatide in nature, present in vegetable fat.

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DISCUSSION

HOWARD A. EDER, M.D., (*New York*): These data suggest the presence of some factor or factors in vegetable fats which can cause reduction of plasma cholesterol.

At the onset it should be noted that these results are at variance with the experiences of Hildreth et al and of Keys et al. These workers demonstrated that severe restriction of dietary fat caused reduction in plasma cholesterol. When vegetable fats were added to the diets of patients on those diets there was a prompt elevation of plasma cholesterol to control levels. The quantity of vegetable fat used was of the same order of magnitude in all these studies. It is possible that the quality differed.

Since the high vegetable fat diet is effective in the presence of animal fats which contain cholesterol it seems likely that explanation of decreased cholesterol intake will not suffice. Plasma cholesterol is probably in equilibrium with cholesterol in the gastro-intestinal tract and with cholesterol in the tissues. The gut equilibrium is of considerable importance since large amounts of free cholesterol are normally secreted into the bile and then reabsorbed by the small intestine. It now is known that fatty acids and bile acids participate in this reabsorption. When either of these groups of substances is absent from the gut, absorption of cholesterol is impaired. It has been suggested that the plant sterols which are not absorbed by the gut combine with fatty acids and remove them from participation in cholesterol absorption. In these diets so high in fat, it would seem that fatty acids would be present in large excess so that the removal of some would be of little overall importance. Certainly one possibility is that these vegetable fats do contain substances which decrease intestinal cholesterol absorption.

Little is known about the mechanisms concerned in the equilibrium between plasma cholesterol and tissue cholesterol. We have recently observed that administration of estrogens causes a decrease in plasma cholesterol while androgen administration will often cause the opposite effect. It seems likely that these hormones affect the tissue equilibrium. Large and rapid shifts in plasma lipid concentration can occur and these must be the result of changes in the plasma-tissue equilibrium. An example of such changes is seen in the data we recently obtained in a mild diabetic with gross hyperlipemia. Twenty-four hours after 20 units of insulin, the plasma neutral fat had fallen from 4,240 mg. per 100 ml. to 318, the plasma cholesterol from 605 to 164, and the plasma phospholipid from 712 to 224. It is a possibility that this vegetable fat mixture contains unknown substances which can act on the plasma-tissue equilibrium.

Since all of the plasma cholesterol is present as a constituent of lipoprotein molecules of relatively constant composition, it is not sufficient to consider plasma cholesterol solely. Changes in plasma cholesterol are in reality reflections of change in lipoprotein concentrations. Since phospholipids are also constituents of these lipoproteins it could be expected that plasma phospholipid concentrations would parallel the cholesterol concentration, as Dr. Kinsell has demonstrated. The changes in the ratio of cholesterol to phospholipid may be a reflection of an altered distribution of lipoproteins.

We should not neglect to emphasize that although a variety of means are now at hand for reducing plasma cholesterol concentration, there is little direct clinical evidence to suggest that doing this has any effect on atherosclerotic disease. Certainly widespread clinical application of these procedures should await more definite proof of their usefulness in human disease.

Trypsin in the Treatment of Local Complications of Peripheral Vascular Disease in Diabetes Mellitus

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Arteriosclerosis obliterans and its complications present major problems in the care of patients with diabetes mellitus. These continue even with the addition of such measures as intra-arterial drugs, sympathectomy and endarterectomy. Search must be made for further aids in therapy if amputations are to be prevented, if more working days are to be saved, and if patient-hospital days are to be reduced.

Recent reports indicate that enzymatic debridement may be beneficial in the treatment of necrotic suppurative wounds[1-11], empyema and hemothorax[12-15], and of respiratory conditions associated with hypersecretion and accumulation of fibrinomucinous material, such as bronchiectasis[16-20]. This study using trypsin in the form of the commercial preparation Tryptar*, was undertaken in cases of diabetes mellitus with local complications usually associated with arteriosclerosis obliterans. The purposes were (1) to observe the clinical effects of trypsin in the treatment of surface ulcers and gangrene, (2) to determine the best method of application of the enzyme and (3) to determine any side effects.

METHOD OF STUDY

Sixteen patients with diabetes mellitus and local complications, 13 of whom had moderate or severe arteriosclerosis obliterans, were observed from August 1951 to June 1952†. All except two were over 40 years of age, and 12 were men. The drug was limited to cases in which there had been two weeks of therapy with measures such as boric acid soaks without any improvement, or no improvement for one or two weeks following an initial benefit. Patients with acute cellulitis without suppuration, or with active local hemorrhage, or known cirrhosis of the liver were not given Tryptar.

The first three patients in the study were given continuous wet dressings of Tryptar solution, prepared from Tryptar powder and the diluent "Sorensen's Phosphate Buffer Solution." Freshly prepared material was applied every three to four hours for three days (although stable in dry form at room temperature, it loses activity after being put into solution). Intermittent soaks also were tried in a few instances. The majority of the 16 patients, however, had their lesions irrigated with Sorensen's Phosphate Buffer Solution, to assure a proper *p*H of the media (*p*H 7) for maximum action of the enzyme, prior to dusting with Tryptar powder. The latter was applied by sprinkling directly from the vial; however, a DeVilbiss Powder Blower No. 119 may be used. After three hours the area was cleansed with normal saline, and then a re-application was made. Usually it was impossible to dust the lesions more frequently than three times daily. Surgical debridement and incision and drainage were done as indicated.

RESULTS

The duration of therapy varied from 2 to 35 days, with the 16 patients receiving a total of 235 days of treatment (Table 1). In four cases, the therapy was given again after a lapse of treatment and the same results were obtained. Since the dosage varied with the size of the lesion and the amount of necrotic material

TABLE 1

Duration of Trypsin (Tryptar) Therapy

No. of Days	1-5	6-10	11-15	16-20	21-35
No. of Patients	2	6	3	1	4

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*Tryptar[R] was supplied by The Armour Laboratories, Chicago, Ill., through the courtesy of Drs. Albert H. Holland, Jr., and Catherine H. Roth.

†Since this study was prepared for publication 10 additional patients have been treated with Tryptar; similar results were obtained.

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present, the minimum single application was as little as 50,000 Armour units and the maximum effective single application, 250,000 Armour units. The daily dose per patient ranged from 100,000 to 750,000 Armour units, and the total dosage ranged from 500,000 to 6,500,000 Armour units (Table 2).

TABLE 2

Total Trypsin (Tryptar) Dosage

Total Dosage (Armour units)	500,000 to 1,000,000	1,250,000 to 1,400,000	2,200,000 to 2,400,000	4,000,000 to 6,500,000
No. of Patients	3	3	4	6

Results were considered "excellent" if complete healing of the lesion occurred and "good" if marked improvement was seen. In this series the results were excellent in 6 cases, good in 6 cases, and poor or no effect in 4 cases (Table 3). The following reports of the 16 cases summarize the clinical data.

Case 1: Sinus tract following spontaneous amputation of the left second toe, because of gangrene in a case with severe arteriosclerosis obliterans. Some decrease in the size of the sinus was noted after treatment with wet dressings. The therapy was discontinued because of slight stinging pain and slight inflammation at the margin of the lesion. *Result—poor.*

Case 2: A large clean ulcer measuring 4 cm. in diameter on dorsum of right foot, in a case with minimal arteriosclerosis obliterans. Tryptar, used as a wet dressing and as a powder, definitely stimulated growth of granulation tissue; there was slight local burning, and redness of the adjacent skin. Subsequently, infection deep in the ventral surface of the foot necessitated amputation which was followed by the appearance of considerable debris in the wound of the stump. Tryptar assisted in cleansing the wound. *Result—good.*

Case 3: Infection secondary to gangrene of right second toe, with moderately good circulation. Tryptar wet dressings aided at first in cleansing the external lesion and soft tissues adjacent to the osteomyelitis. After incision and drainage of the metatarsal area, the wet dressings of the enzyme assisted in cleansing the wound and in closure. A follow-up several months later revealed no recurrence. *Result—good.*

Case 4: Large indolent ulcers measuring 3 cm. in diameter over both tibia, with severe arteriosclerosis obliterans. Continuous wet dressings were used for three days (total of 1,250,000 Armour units for both legs)

TABLE 3

Analysis of cases treated with trypsin (Tryptar)

Case No.	Diagnosis	Days Treated	Total Dosage (Armour Units)	Results and Comments
1	Sinus following amputation of gangrenous toe; severe arteriosclerosis	7	2,200,000	Poor results; therapy interrupted because of local stinging pain; drug administered by wet dressing only.
2	Ulcer of foot; necrotic amputation stump; minimal arteriosclerosis	29	6,000,000	Good
3	Ulcer of toe secondary to gangrene; good circulation	15	4,400,000	Good
4	Ulcers on both legs; severe arteriosclerosis	3	1,250,000	Poor; therapy interrupted; patient died.
5	Persistent sinus following gangrene of foot; thigh amputation	6	2,400,000	Excellent
6	Persistent sinus following spontaneous toe amputation	13	1,300,000	Excellent
7	Persistent sinus following incision and drainage of infectious gangrenous foot	22	4,000,000	Excellent
8	Sinus following gangrene of foot with thigh amputation	8	800,000	Good
9	Gangrene of toe	18	4,500,000	Excellent
10	Ulcer over leg fracture; fair circulation	10	1,000,000	Excellent
11	Gangrene of toe with ulcer	34	4,250,000	Good
12	Supracondylar amputation stump without primary closure	10	2,250,000	Good
13	Chemical burn eschar of leg	9	2,250,000	No effect; enzyme does not act on eschar itself.
14	Abscess and ulcer of thigh; good circulation	2	500,000	No effect
15	Stasis ulcers of leg; varicose veins	14	1,400,000	Good
16	Ulcer of foot; osteomyelitis; good circulation	35	6,500,000	Excellent

without beneficial effect; the skin surface was slippery to touch. Subsequent follow-up was impossible because the patient died of a coronary thrombosis. *Result—poor.*

Case 5: Persistent sinus following thigh amputation because of gangrene of foot, and severe arteriosclerosis obliterans. Following application of Tryptar the sinus closed with such an excess of granulation tissue that it required excision. *Result—excellent.*

Case 6: Sinus at site of spontaneous toe amputation. This sinus had persisted for four months while on such treatment as boric acid soaks. After 13 days of Tryptar treatment, the sinus completely closed. *Result—excellent.*

Case 7: Gangrene and infection of foot treated by incision and drainage with persistence of a small sinus. Tryptar treatment was given for 22 days, when suddenly drainage ceased and the sinus closed. Follow-up several months later revealed no recurrence. *Result—excellent.*

Case 8: Sinus following a mid-thigh amputation. Tryptar was applied with resultant closure of the sinus and excess granulation tissue. This area had to be reopened because the sinus closed superficially. *Result—good.*

Case 9: Gangrene of a right toe (not extending to the metatarsophalangeal joint), and previous amputation of the left foot. Tryptar, applied at the border between the necrotic and more normal appearing tissue, provided a line of cleavage with a base of granulation tissue. The toe eventually amputated spontaneously and a good area of granulation tissue followed Tryptar treatment. It was noted later that the granulation tissue covered a small pocket of debris; this was removed surgically. *Result—excellent.*

Case 10: Ulcer measuring 3 cm. in diameter over fracture of left leg, with fair circulation. Following mechanical debridement and application of Tryptar a film of granulation tissue was obtained across the defect. *Result—excellent.*

Case 11: Gangrene of right fifth toe with draining ulcer. Tryptar was applied with moderate results. Granulation tissue was evident and the lesion was healing well when seen several days after treatment. *Result—good.*

Case 12: Supracondylar amputation stump without primary closure. Tryptar treatment resulted in the appearance of granulation tissue and a much cleaner wound within three days. This continued until healing. *Result—good.*

Case 13: Chemical burn from unknown liquid with an eschar on the leg; severe arteriosclerosis obliterans. Tryptar was applied topically as a solution without perceptible improvement. *Result—no effect.*

Case 14: Abscess of left thigh with an external ulcer measuring 2 x 0.5 cm.; circulation good. Two vials of Tryptar applied as a solution. *Result—no effect.*

Case 15: Two stasis ulcers, each 2-3 cm. in diameter, covered with slight serous discharge on right leg, with varicose veins. Ulcers slowly filled over with scar tissue, apparently stimulated by Tryptar. *Result—good.*

Case 16: Infected ulcer of right foot at base of third toe with extension of infection to plantar surface of foot. After incision and drainage of a wide area, Tryptar was applied with excellent results. The lesion filled in with granulation tissue, and only a small sinus remained at the plantar surface. The patient refused resection of the infected metatarsophalangeal joint and went home. *Result—excellent.*

DISCUSSION

It is difficult to interpret the results of a clinical study when variables, such as differences in nutrition (including vascular supply), diabetes, and bacterial contamination are present. Likewise, a control study is difficult, since it is almost impossible to secure patients whose lesions and general conditions are exactly comparable to each other. Since rest, soaks and time appear to benefit many patients with peripheral vascular complications, the drug was limited to those individuals who had had two weeks of therapy with measures such as boric acid soaks without any improvement, or had no improvement for one or two weeks following initial benefit.

The frequency and diligence of application as well as the method of administration influence the results. In Case 1, irrigation with Tryptar solution or insertion into the sinus of soft gelatin capsules containing the powder would have provided more direct contact of the enzyme with the necrotic tissue, than did the use of wet dressings. Since Tryptar does not act on eschars, as noted in Case 13, the solution should be administered by hypodermic infiltration into the necrotic tissue immediately beneath the eschar, much as one would infiltrate with a local anesthetic agent. It has been stated[21] that frequently the edges of the eschar can be slightly raised and a cotton-tipped applicator, saturated with Tryptar solution, rotated beneath the edges of the eschar to effect a good plane of cleavage.

Recognizing the aforementioned limitations of such a study the following impressions of trypsin (Tryptar) appear valid:

1. Trypsin assists the growth of granulation tissue. In some instances formation of granulation tissue was so excessive that it prematurely closed a sinus tract.

2. The material may be an aid in cleansing infected

ulcers and amputation sites; it is only auxiliary to surgical excision and does not replace surgical measures in removing necrotic debris.

3. Trypsin appears to be especially helpful in the closing of short sinuses such as at the site of spontaneous amputation of a single toe.

4. Trypsin appears to assist in delineation of the borders of necrotic or gangrenous lesions.

5. Dusting the powder on lesions is the simplest and most effective method of applying trypsin if the lesion is easily accessible, and if it is moist or is previously irrigated with the diluent, Sorensen's Phosphate Buffer Solution. The use of a powder blower permits even distribution of the material and aids it in reaching crevices containing necrotic material. The amount of the drug required depends on the size of the lesion; in this series of patients the dosage was 50,000 to 250,000 Armour units, three or four times daily.

6. Trypsin in a few instances caused a moderate local burning sensation; it has been stated that this can be controlled by the administration of an antihistamine such as Benadryl[R], or by the incorporation of 1 per cent procaine hydrochloride in the trypsin solution[21]. No other side effects were noted, and no evidence of sensitivity or antigenicity was observed.

CONCLUSIONS

Based on the clinical results obtained in 16 patients receiving topical applications of trypsin, it appears that the preparation may be an aid in the treatment of complications of peripheral vascular disease in diabetes mellitus. The enzyme appears to facilitate the growth of granulation tissue and may aid in cleansing infected ulcers, amputation stumps and sinuses.

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Renal Papillary Necrosis

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INTRODUCTION

Acute destruction of the renal papillae without suppuration within the affected segment is a rarely reported but disastrous renal complication of diabetes mellitus. It may also occur in the nondiabetic as a rare sequel of obstructive uropathy. This disease was first described in 1877 by von Friedreick[1] but it is still infrequently recognized. The purpose of this paper is to call attention to the entity and to describe the gross and microscopic appearance of the lesion.

DEFINITION

Renal papillary necrosis or renal medullary necrosis are appropriate and interchangeable names for this pathological condition. Less desirable synonyms are necrotising pyelonephritis[2], papillitis renis necroticans[3], Gunther's disease[4], diphtheria of the papillae[5] and papillitis necroticans[6].

The reported frequency of renal papillary necrosis at autopsy varies from 3 to 5 per cent in diabetic patients and is less than 0.1 per cent in nondiabetic patients[4,7,8]. In autopsied diabetic patients with acute pyelonephritis, about 27 per cent have papillary necrosis. In our series, out of the total of 1812 post mortem examinations performed on patients over twenty years of age from 1940 through November 1952 there were 97 cases of diabetes mellitus. Twelve of the nondiabetic patients had acute pyelonephritis, and of these only three had papillary necrosis. Thus the incidence of the disease complicating acute pyelonephritis was twice as great in the presence of diabetes. All of the patients with papillary necrosis were over 60 years; 11.3 per cent of female diabetics and 9.2 per cent of all diabetics in this age range showed the lesion. Comparable figures for nondiabetics are 0.41 per cent and 0.27 per cent respectively. The greatest incidence was found in the seventh decade. (Table 1). Table 2 presents the actual number and percentage of diabetic patients with this kidney lesion according to age and sex. It is important to note that all of the diabetics with the lesion were women.

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PATHOGENESIS

Little is known of the pathogenesis. It has been noted previously that the lesion rarely arises in the nondiabetic in the absence of urinary tract obstruction[4,8,10]. The most acceptable theory is that which postulates an ischemia of the medullary portion of the medulla—an ischemic infarct[4,9,10,11]. The appearance of the lesion is that of such an infarct. The weakness in this theory is the absence of knowledge concerning the cause of the decreased blood flow to the papilla. Some believe coalescence of abscesses at the base of the medulla is responsible[7]. Others postulate increased arteriosclerosis burdening the normally smaller blood supply of the medulla[4,12,13].

Extrinsic pressure arising from increased hydrostatic pressure in the tubules secondary to obstruction has been postulated as the causative factor, particularly in the

TABLE 1

Incidence of papillary necrosis in diabetics and nondiabetics with acute pyelonephritis

Group	Total	Number with acute Pyelonephritis	Percentage of total with acute Pyelonephritis	Number with Papillary Necrosis	Percentage of total cases with Papillary Necrosis	Percentage of acute Pyelonephritis with Papillary Necrosis
Diabetics	97	14	14.4	7	7.2	50%
Non-diabetics	1715	12*	0.7	3	0.17	25%

*Only 12 were sufficiently severe to be of importance

TABLE 2

Age and sex incidence of papillary necrosis in diabetics

Age	Total Number	Male		Female		Total Per cent
		Number of Cases	Papillary Necrosis	Number of Cases	Papillary Necrosis	Percentage
50-59	11	8	0	3	0	0
60-69	31	11	0	20	2	10	6.6
70-79	30	1	0	29	4	13.8	13.3
80-89	15	2	0	13	1	7.6	6.6

nondiabetic[8,10,14,15]. Experimental procedures in animals have yielded equivocal results. It has been reported that ligation of the ureter and injection of bacteria intravenously has been followed by appearance of the lesion[7,10]. For some years it has been known that vinylamine can affect the kidneys, in this way; Mandel and Popper[16], using this drug, noted hyperemia in the medullary portion and ischemia in the cortex. They believed that the ensuing necrosis of the papillae arose from the thrombi formed during the stage of hyperemia. Borland and Jackson[17] observed the appearance of the lesion in rats maintained upon a fat-free diet. On the other hand, attempts to produce it in the same animal by ligation of the ureter and injection of bacteria into the ureter have been unsuccessful[4]. Retrograde pyelography has been implicated[18]; one patient in this series died three days after this procedure. Para-amyloid deposits and diabetes itself, because of the increased acidity of the tissues depressing the leukocyte response, have been implicated[4, 10, 13]. Some authors have implied a relation between the disease and intercapillary glomerulosclerosis[4, 18]. In this series there were but two patients with intercapillary glomerulosclerosis. Three patients had cortical infarcts. All had arteriosclerosis and eight had arteriolosclerosis as well. Table 3 shows the distribution of these lesions.

TABLE 3
Associated Kidney Lesions

Case No.	Diabetic	Age	Sex	Acute Papillary Necrosis	Healed Papillary Necrosis	Acute Pyelonephritis	Intercapillary Glomerulosclerosis	Infarcts	Arteriosclerosis	Arteriolosclerosis
174364	Yes	79	Female	x		x	x		x	x
181766	Yes	63	Female	x		x			x	x
185351	Yes	78	Female	x		x	x	x	x	
189774	Yes	74	Female	x		x		x	x	x
22171	Yes	60	Female	x		x			x	x
29546	No	76	Male	x		x			x	x
16480	Yes	85	Female		x	x			x	x
64657	No	81	Female		x	x		x	x	x
65264	Yes	72	Female	x		x			x	x
63930	No	61	Female	x		x			x	

PATHOLOGY

Grossly, the kidney is usually normal in weight except when ureteral obstruction produces an edematous, boggy, purulent mass. The cortex may or may not have abscesses within it. In our series the kidneys, since they came from elderly people, all had granular cortices with retention cysts characteristic of arteriosclerosis. The medullary portion has gray or gray-yellow streaks in the papillae. Within an affected papilla there is a semicircular arc of this gray-yellow material which marks the boundary between necrotic and less affected tissue. Distal to this arc the medulla is homogeneously gray-yellow, while proximally there is a slight hyperemia. Microscopically, there is a coagulation necrosis of the distal part of the affected papilla. A definite border separates the coagulated part from the relatively more healthy portion of the medulla. This border is composed of mononuclear cells and polymorphonuclear cells of varying proportions depending upon the stage of the disease. Within the necrotic portion, the nuclei are pyknotic or absent. The tubules are usually not dilated, but clumps of bacteria and cellular debris may be present within them. In our series few thromboses of the small vessels were seen. The columns of Bertini are not involved in the necrosis, although abscesses may be found within them. Gross inspection of a stained section reveals the distinction between the pale necrotic and darker non-necrotic parts with the deep blue border in the middle. Specifically, only those kidneys in which the affected papillae show maintenance of the normal architecture, although with varying degrees of loss of cellular detail, are to be considered as instances of papillary necrosis unless the papillae have sloughed off.

In healed lesions the papilla is shortened with a blunt tip. There is absence of the semicircular arc between the necrotic and non-necrotic portions. Histologically, the tip of the papilla is pale and ischemic with replacement of tubules by fibrous tissue. A few enlarged collecting tubules are present within which an occasional clump of bacteria may be found. The border of mononuclear and polymorphonuclear leukocytes is absent or greatly decreased. Elsewhere in the kidney varying degrees of acute and chronic pyelonephritis are present.

CASE REPORTS

Case 1. A 72-year-old white woman, who had had diabetes mellitus 22 years, entered the hospital complaining of nausea, vomiting, sweating, shaking and abdominal cramps of one week's duration. She had been in the hospital three weeks before for removal of a cataract from the left eye. The tests for sugar in the urine had been variable on this previous admission and the blood sugar varied from 99 to 358 mg. per 100 cc. The urine contained 15 to 20 white blood cells per high power field. She had been sent home on a weighed diet and advised to use 40 units of NPH insulin daily. She had had no dysuria, nocturia, hematuria, urgency, frequency or incontinence.

At the time of the second admission to the hospital the general physical examination did not show any important abnormality. Her temperature was 98.6°F. The laboratory findings were as follows: blood sugar, 438 mg. per 100 cc., carbon dioxide combining power, 52 volumes per cent, leukocyte count, 26,000, erythrocyte count, 3,520,000, hemoglobin, 9.5 gm., albuminuria graded 1 plus, glycosuria graded 2 plus, specific gravity of the urine 1.010, urinary sediment containing 5 to 8 white blood cells and many red blood cells per high power field. The clinical impression was possible myocardial infarction in an emotionally unstable woman.

The initial treatment included the intravenous infusion of fluids and in addition administration of insulin. The tests of the urine showed no sugar or only a trace of sugar after the initial examination. The morning after admission, the blood sugar was 516; the urine at this time contained sugar graded 4 plus. The non-protein nitrogen of the blood was 62 mg. per 100 cc., the serum calcium was 5.1 mEq/L. The serum proteins were 5.8 gm. per 100 cc. The patient complained of cramping abdominal pain. The heart beat was irregular and there was a radial pulse deficit. The electrocardiogram showed auricular fibrillation; there were no signs to indicate infarction. Roentgenograms of the chest showed enlargement of the heart; the lungs were clear but there was enlargement of the thyroid gland with calcification. The films of the abdomen showed no sign of gall stones, renal calculi, distention of the bowel or fluid level. After treatment with quinidine the heart beat became regular. The fever and prostration continued.

On the third day, the urine became creamy with pus. The temperature fell to normal and the patient said that she felt better. It was thought that the patient had had a urinary tract obstruction which had spontaneously drained itself. Subsequent examination confirmed the presence of a mass which was now laterally placed. A bilateral retrograde pyelogram showed normal appearance of the kidneys. E. coli was cultured from urine from the left kidney. The next day the temperature rose to 102. The blood sugar was 147, non-protein nitrogen 91.9, carbon dioxide combining power 40 vol. per cent, potassium 5.7 mEq/L, chlorides 90 mEq/L, and sodium 122 mEq/L; the white blood cell count was 31,000.

An exploratory laparotomy was performed. The abdomen contained a small amount of clear fluid. Both kidneys were moderately enlarged but no evidence of a perinephric abscess was noted. The abdomen was closed without drainage. About one hour after exploration the patient became comatose and expired while in the anesthesia recovery room.

Post mortem examination revealed a bilateral pleural effusion, passive congestion of the liver, atherosclerosis of the aorta, chronic cystitis, and senile atrophy of the cerebral cortex without hemorrhage or infarction. The kidneys were enlarged and soft and showed a massive acute papillary necrosis with sloughing of some of the papilla. Microscopically, all the papillae sectioned showed papillary necrosis.

Case 2. A 78-year-old white woman with diabetes mellitus of five years' duration entered the hospital from a nearby nursing home. She had had nausea beginning seven to ten days before, vomiting for three or four days, and stupor of one week's duration. The diabetes had been poorly controlled and two months previously the right leg had been amputated because of diabetic gangrene. Three weeks previously she had had several days of chills and fever; pus had been found in the urine. She was told she had cystitis and given a sulfonamide drug. The pyuria and fever subsided in three days but recurred three or four days before admission.

Her temperature was 101, the pulse 96, the respiration 24 and the blood pressure 136/80. The abdomen was soft, non-tender, and there were no palpable masses.

It was thought that in addition to the diabetes she might have had a cerebral vascular accident. The laboratory data were as follows: leukocyte count, 18,400; hemoglobin, 12.5 gm.; erythrocyte count, 4,130,000; non-protein nitrogen, 37 mg. per 100 cc.; blood sugar, 263; carbon dioxide combining power, 52 vol. per cent; blood sulfadiazine, 6.2 mg. per cent. The urinalysis showed the specific gravity, 1.026, no sugar, albumin graded 2 plus, two to three white blood cells per high power field, no red blood cells, no casts or bacteria. The culture of the urine was negative.

A weighed diet and insulin were given. Urinalysis at 6-hour intervals showed absence of sugar and red blood cells with an occasional white blood cell. The patient remained lethargic and on the third day developed aphasia and right hemiplegia. On the fourth hospital day, a lobular pneumonia occurred. The patient began to have Cheyne-Stokes respiration and expired.

At the post mortem, there was found acute bacterial endocarditis of the mitral valve, adhesive pericarditis, right hydrothorax, lobular pneumonia, multiple myocardial abscesses, multiple cerebral abscesses, atrophy of the cerebral cortex and multiple renal abscesses plus bilateral renal infarcts. The medullary portions contained several abscesses. The examination of the kidney showed that sections of the papillae were ischemic with dilated

tubules in which small clumps of bacteria were present; a ring of round and polymorphonuclear cells separated the necrotic papillae from the rest of the medulla.

DIAGNOSIS

The diagnosis of renal papillary necrosis is difficult. In the absence of passage of a papilla in the urine it is almost impossible. Retrograde urograms may help if structural changes have occurred which increase the size of the minor calyces or produce negative shadows in the larger calyces or pelvis due to sloughing of the papillae[21]. In the early stages or in those cases in which no sloughing has occurred the urogram may appear normal[21]. Symptomatology mentioned includes hematuria, pyuria, flank pain, azotemia, albuminuria, dysuria, urgency, frequency, chills, fever, nausea, vomiting, stupor and elevation of the white blood cell count. These are but the symptoms and signs of acute pyelonephritis.

In our series one-half of the patients on admission had stupor or coma, nausea and vomiting. All had leukocytosis and depression of the carbon dioxide combining power to acidotic levels. The nonprotein nitrogen was elevated in all cases. In all but two cases, the urine contained only a few white blood cells and red blood cells on admission. One-half had normal temperature and only three complained of chills. The symptoms and signs of the admitting illness too often obscured the urinary tract lesion.

TREATMENT

Therapy employing large doses of the antibiotics would appear to be the only rational course for the diabetics since the disease is so often bilateral. One of the two patients in our survey having demonstrable healing had received large doses of antibiotics. Relief of ureteral obstruction, of course, is indicated if present. Some consider nephrectomy as life-saving in those cases in which the diagnosis of unilateral disease is made [4,8,9,10].

A realistic approach to the problem of diagnosis and therapy requires awareness of the possibility of the lesion and search for urinary tract infection in the complicated diabetic.

DISCUSSION

The reason for the relative rarity of renal papillary necrosis lies in the failure of recognition of the lesion, namely an ischemic coagulation necrosis of the papillae which are surrounded by a border of mononuclear and polymorphonuclear cells. The lesion will be missed if the examiner's attention is focused upon the surrounding acute pyelonephritis with its bacteria and white blood cells, and if sections are not taken through the papilla. In a six-month period at this hospital three instances of this disease were found at post mortem. This prompted a review of all the autopsies on diabetics during the past thirteen years. A similar review was made of all patients who had a post mortem diagnosis of pyelonephritis. From this series of 1812 autopsies seven additional cases of this lesion were found.

One additional case, in which the gross description of the kidney was suggestive, could not be considered because adequate sections of the papilla were not available.

Nine of the ten patients were women. The one male patient and one of the two nondiabetic female patients had unilateral lesions with ipsilateral obstruction of the ureter. The difference in sex incidence of urinary tract infections in the female may be a factor.

It is apparent that there is a paucity of diagnostic signs and symptoms. Symptoms such as chills and fever, urinary frequency and localized tenderness, pyuria and elevated white blood cell count and nonprotein nitrogen suggest an infection of the urinary tract, but do not necessarily indicate papillary necrosis. Frequently the symptoms and signs of the primary illness tend to obscure the urinary tract pathology. Furthermore, the signs and symptoms may change during the course of the illness.

SUMMARY

Renal papillary necrosis, although infrequently reported, is a much more common lesion than is supposed. Reasons for the failure to recognize the lesion both clinically and pathologically are presented. The difficulties in diagnosis are emphasized and illustrated by two case histories.

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Protein Metabolism in Disease

Clinical proteinology may be said to begin with Müller, who in 1884 reported his work on nitrogen metabolism in typhoid fever. Subsequently, cancer, erysipelas, pneumonia, and tuberculosis were studied by, respectively, Müller, Riethus, Von Leyden and Klemperer, and Ott. From these studies came the term "toxic destruction of proteins." That fever per se does not cause this "toxic" destruction was shown by Graham and Poulton. This first spurt of interest in protein also included the study of the protein needs of pregnant and nursing women, while in pediatrics, as early as 1905, Rubner and Heubner reported on the protein metabolism of the growing child.

The prevalence of famine in various parts of Europe during World War I gave impetus to observations by many workers on the effects of starvation, including the relationship between the level of blood proteins and edema.

In the interval between the two wars, some studies on various aspects of proteinology continued, with the development of new techniques and the perfection of old ones. New and important concepts were also formulated. Among these may be mentioned the studies of Van Slyke et al on amino acids, of Whipple et al on blood proteins and hemoglobin formation, and their concept of the dynamic state of body constituents, later to be confirmed by Schoenheimer by the use of isotopes.

Important techniques for determination of the fluid compartments of the body, of the circulation time, electrophoresis, a roentgenologic method for the determination of heart size, new psychologic tests, and a better comprehension of endocrinology, particularly of the adrenal cortex, were developed. Cuthbertson's findings of increased azoturia following fractures extended the concept of "toxic destruction of proteins" to the field of traumatology, and the studies of Ravdin and his group on the relation between wound dehiscence and hypoproteinemia awakened clinical interest in protein involvement in disease. Meanwhile, the more general writings of McLester and of Youmans laid the foundation for a better appreciation of the role of nutrition in disease.

World War II gave a new impetus to protein and other nutritional studies. Ancel Keys' Minnesota project, which may be considered as an up-to-date, "streamlined" counterpart of the project of Benedict and his colleagues of the Carnegie Laboratory of Nutrition, collected an encyclopedic mass of knowledge and clarified a large area of the phenomenology of starvation. The observations of Walters et al on Japanese-held Indian prisoners of war, of the starvation team in Holland, and of Mollison on the inmates of the Belsen concentration camp, supplemented and extended the observations of the Minnesota investigators.

From "Review: The Fundamentals of Clinical Proteinology" by Co Tui, M.D., in *The Journal of Clinical Nutrition.* March-April 1953.

The Effect of the Hyperglycemic Factor on the Metabolism of Glucose by the Extrahepatic Tissues

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The hyperglycemic-glycogenolytic factor (HGF) of the pancreas brings about a rise in blood sugar when administered to the intact animal. The rise in blood sugar results in part at least from glycogenolysis of liver glycogen[1]. There are other observations which have raised the possibilities of other actions of this hormone. Alloxan-diabetic dogs have a markedly increased insulin requirement, which decreases sharply when the pancreas is removed[2,3]. According to one view, the alloxan destroys the insulin producing beta cells but leaves the HGF-secreting cells intact. The subsequent pancreatectomy removes this source of HGF and, as a result, the insulin requirement is reduced. It is difficult to see how such an action of HGF can be explained on the basis of its glycogenolytic action alone. The alloxan-diabetic dog has a marked reduction in utilization of carbohydrate, which can hardly be explained by an inadequacy in temporarily storing it as liver glycogen. In this type of diabetes there appears to be a reduction in capacity either to oxidize glucose or to convert it to storage forms such as fat. Since these are functions largely controlled by insulin, this could indicate an insulin antagonist action of HGF. By using the eviscerated-nephrectomized rabbit as the test preparation, we have attempted to ascertain if HGF antagonizes the action of insulin. With the aid of C^{14} labeled glucose we have determined the effect of HGF on glucose oxidation in addition to its effect on glucose disappearance.

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We are indebted to the Lilly Research Laboratories for the insulin and HGF used in this work.

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METHODS

The general plan of the experiments was similar to that used before in these laboratories and described in previous papers[4,5]. Non-fasted rabbits were eviscerated and nephrectomized. Three types of experiments were carried out. In the first series, the eviscerated animals were maintained with maximum insulin activity (20 units per hour). In the second, a low insulin activity was maintained by the injection of 0.1 unit per hour; in previous tests it was found that 0.1 unit per hour was about the smallest dose that would have a measurable action on glucose disappearance. In the third group no insulin was administered. Comparable control groups which did not receive HGF were used for each of the above types of experiments.

In all experiments the eviscerated rabbits were given at the beginning a priming dose of C^{14} uniformly labeled glucose so as to make the specific activity of the body circulating glucose the same as that of the glucose to be used for the subsequent injections. The blood sugar concentration was then maintained at a normal level throughout the experiment by the injection of C^{14} uniformly labeled glucose. In the test animals a priming dose of the HGF was given intravenously at the start of either the fourth or fifth hour, and this dose was given each hour for three hours thereafter by continuous injection. The dosage of HGF administered (Table I, II) was from 0.1 to 0.9 mg. per kg. per hr. Larger amounts of material appeared to have a toxic effect on the animals. The sample of HGF used in this work (Lilly 208-108B-169A) was reported to contain no

more than 0.005 units per mg. of insulin and to give in the rabbit a 30 mg. per 100 cc. rise in blood sugar when 15 to 30 μg. per kg. were administered intravenously.

The glucose disappearance or glucose transfer rate (that is, transfer of glucose from the extracellular to the intracellular compartment) was calculated from the amount of sugar required to maintain a normal blood sugar concentration before and after the administration of the HGF. The fraction of the total metabolism supplied by the oxidation of glucose was obtained by collecting the expired carbon dioxide and comparing its specific activity with that of the injected glucose. For comparison purposes, identical calculations were made for the control groups using comparable time periods.

RESULTS

The results are given in Tables I and II. The HGF has a definite effect on the glucose disappearance rate. This effect appears to be more pronounced in the insulin treated animals. It has been our experience in the past with our eviscerated animals that the sugar disappearance rate never goes down but usually increases slightly with time, and this is shown to be the case in the control animals reported here. On the other hand, in these experiments the administration of HGF decreased the disappearance rate of glucose in all experiments except in animal No. 12 (a non-insulin experiment).

There is a decrease of output of carbon dioxide in some of the test animals after injection of the HGF, but this is no more pronounced than in the control animals for a comparable period. There is no detectable difference between the test and control groups in the fraction of carbon dioxide coming from the injected glucose.

DISCUSSION

The data reported here indicate that the HGF reduces to some extent the rate of transfer of glucose from the blood into the cells, particularly when this has been accelerated by insulin. This occurs despite the presence of maximum amounts of insulin. The administration of HGF has little or no effect on the oxidation rate of glucose. This is in keeping with the view that the action of insulin is on glucose transfer and not on the intracellular enzyme system concerned with the oxidation of glucose[6].

Eventually the reduction in glucose transfer might affect its oxidation rate. However, glucose on entering the cell is diluted by a metabolic pool which retards its combustion to carbon dioxide so that when the blood glucose is maintained at a constant specific activity, it takes 5 to 8 hours for the specific activity of the carbon dioxide to attain a constant level[4]. Increasing or decreasing the amount of glucose entering the cell does

TABLE 1

*The effect of the hyperglycemic-glycogenolytic factor on the metabolism of glucose in eviscerated animals treated with insulin**

		HGF + Maximum insulin				HGF + Tracer insulin			Maximum insulin controls	
Exp. No.		1	2	3	4	5	6	7	8	9
Per cent of expired carbon dioxide from injected glucose	1st hr.	8	8	12	—	—	—	—	11	6
	2nd hr.	17	19	26	15	21	—	12	27	16
	3rd hr.	29	31	33	28	30	—	19	37	22
	4th hr.	31	31	37	37	38	—	23	39	30
	5th hr.	33	40	39	47	40	—	28	43	39
	6th hr.	35	40	42	46	42	—	30	39	39
	7th hr.		42	50	49	46	—	32	43	42
Glucose utilization (mg. per kg. per hr.) before HGF injection		392	405	540	470	378	279	256	450	430
after HGF injection		346	216	425	445	336	155	226	465	460
Carbon dioxide expired (mg. per kg. per hr.) before HGF injection		789	777	1040	1030	920	1033	610	760	1040
after HGF injection		415	873	770	1050	665	541	635	575	790
HGF dosage (mg. per kg. per hr.)		0.9	0.8	0.7	0.1	0.19	0.6	0.10		
Animal Wt. (kgs.)		1.15	1.19	1.33	1.1	1.33	1.70	1.18	1.15	1.20

*HGF injected at the beginning of the fifth hour in Experiments 1-7 inclusive.

TABLE 2

*The effect of the hyperglycemic-glycogenolytic factor on the metabolism of glucose in eviscerated animals not given insulin**

Exp. No.	HGF — No insulin			No insulin controls		
	10	11	12	13	14	15
Per cent of expired carbon dioxide from injected glucose 1st hr.	6	5	—	6	4	7
2nd hr.	18	13	12	9	7	9
3rd hr.	16	16	15	13	10	12
4th hr.	17	17	17	13	11	16
5th hr.	18	17	18	16	13	20
6th hr.	19	—	19	18	15	22
7th hr.	20	22	20	22	19	25
8th hr.	22			—	—	
Glucose utilization (mg. per kg. per hr.)						
before HGF injection	201	172	180	173	191	176
after HGF injection	167	166	183	213	268	182
Carbon dioxide expired (mg. per kg. per hr.)						
before HGF injection	1010	955	775	640	710	450
after HGF injection	632	520	640	480	530	370
HGF dosage (mg. per kg. per hr.)	0.7	0.25	0.25			
Animal Wt. (kgs.)	1.5	1.2	1.0	1.80	1.98	1.86

*HGF injected at the beginning of the sixth hour in Experiment 10, and at the beginning of the fifth hour in Experiments 11 and 12.

have some effect on the amount of glucose oxidized, but the effect is brought about quite slowly and needs several hours to become fully evident. The reduction in transfer of glucose into the cell brought about by the H-G Factor is not large and would need several hours to affect the oxidation rate of this compound. Over the course of days the HGF could depress significantly the amount of glucose transferred into the cells of the extrahepatic tissues. This would, in the long run, decrease the oxidation and storage of glucose by these tissues.

Our findings add support to the view that the HGF may play a role in some types of clinical diabetes. In these patients there is no evidence of a reduction in the production of insulin, but they appear to suffer from an overproduction of some insulin antagonist. Patients who have been depancreatized need less insulin than do many cases of clinical diabetes[7,8,9]. The relative mildness of their diabetes could be due to the fact that the source of the HGF has been removed with the source of insulin. Our findings indicate that an overbalance of the HGF would lead to a reduced utilization of glucose by the extrahepatic tissues which would contribute to the severity of the diabetic condition.

Our results also indicate that the HGF does not act directly on the oxidative processes carried on by the extrahepatic tissues. Its direct and immediate action is not to decrease the oxidation of glucose or to increase the oxidation of fuels that compete with glucose. If the HGF had such actions in the intact animal, they would have to be mediated through the liver. If the HGF increased the production of competitive fuels by the liver, this could lead to an increase in oxidation of them by the extrahepatic tissues[10].

SUMMARY

The effect of the hyperglycemic-glycogenolytic factor (HGF) on glucose metabolism has been studied in eviscerated-nephrectomized rabbits receiving low, and high, doses of insulin, and in other experiments, no insulin.

The administration of the HGF decreased the transfer rate of glucose from the extracellular to the intracellular compartment. It is unlikely that the HGF has a direct action on glucose oxidation. Since it decreases glucose transfer, it ultimately would decrease glucose oxidation indirectly.

The hyperglycemic-glycogenolytic factor may be considered an insulin antagonist in the extrahepatic tissues since it counteracts the influence of insulin which increases the glucose transfer rate.

ADDENDUM

Since submission of this article for publication, the proceedings of the Conference on Hormone Factors in Carbohydrate Metabolism of the Ciba Foundation Col-

loquia on Endocrinology, Vol. 6, Page 233, 1953 (J. & A. Churchill Ltd., London) has appeared. This contains the report of Dr. J. L. R-Candela regarding his observations on the effect of the hyperglycemic factor on insulin action in the isolated diaphragm. In confirmation of our work, his data indicate a marked inhibition of insulin action by an extract of the pancreas of alloxanized animals.

Acknowledgment is given to the assistance of Mary L. Butler and Caryl W. Stortz.

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Metabolic Hypoglycemia and Food Intake in Man

Previously reported studies on animals have shown that experimentally induced alterations in level of blood glucose significantly modify food intake. These results provided a basis for formulation of the "glucostatic" theory of food intake regulation. Briefly, this theory postulates that, in the normal animal, variations in the blood glucose level exert a regulatory influence on food intake. Other experiments have indicated that a hypothalamic center may mediate between blood glucose levels and food intake.

In order to extend the glucostatic theory to include conditions associated with abnormal levels of blood sugar, such as diabetes mellitus, the concept of "effective" blood sugar levels has been proposed, and has been applied to alloxan diabetes in the rat, and the hereditary obesity-diabetes syndrome in the mouse.

"Effectiveness" of blood glucose denotes its ability to enter into cells. Arteriovenous glucose differences largely measure removal of glucose by tissues and, accordingly, may be regarded as an index of the effectiveness of blood glucose. For example, in uncontrolled diabetes mellitus, arteriovenous glucose differences are frequently negligible and thus hyperglycemia and "metabolic hypoglycemia" may be said to coexist. Since arteriovenous glucose differences may provide information concerning tissue removal of blood sugar at a given arterial level, such differences, according to the glucostatic theory, should enhance correlation of arterial glucose levels with food intake, and feelings of "hunger" or "satiety."

It is acknowledged at the outset that feelings involving desire for food are not in any sense quantifiable. Yet they represent a conscious expression of one of the most precise regulatory devices in biology—the mechanism which regulates energy balance. Moreover, any theory which attempts to explain food intake regulation and which cannot account for feelings of hunger is necessarily inadequate. Thus, a correlation, however imprecise, between feelings of hunger, or absence of such feelings, and values which are indices of carbohydrate utilization is justifiable as a first approximation.

Regardless of the complex homeostatic forces which condition glucose uptake by cells, shrinkage of the peripheral arteriovenous glucose difference in the normal subject ordinarily represents a response to carbohydrate depletion. Since hunger similarly has been postulated to be a response to "metabolic hypoglycemia," a correlation in time between the two might be anticipated.

From "Arteriovenous Glucose Differences, Metabolic Hypoglycemia and Food Intake in Man," by Theodore B. Van Itallie, M.D., Rachel Beaudoin, D.SC., and J. Mayer, Ph.D., D.Sc., in *Journal of Clinical Nutrition*, March-April 1953.

Hyperinsulinism due to Islet-Cell Tumors Simulating Sarcoma

A Report of Two Cases of Large Tumors Composed of Round and Spindle Cells Associated With Hypoglycemia

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Functioning islet-cell tumors are usually composed of nests, cords, or sheets of cells, resembling beta cells and associated with varying amounts of intercellular stroma. Such tumors are usually small. In contrast, we have observed two very large neoplasms which caused hypoglycemia and were composed predominantly of spindle-shaped cells with cytoplasmic processes. Associated with these spindle cells in both of the tumors were round cells without cytoplasmic processes. The purpose of this paper is to describe the clinical features and pathologic findings of these two cases in order to substantiate the thesis that these tumors are actually functioning islet-cell neoplasms.

REVIEW OF THE LITERATURE

To the best of our knowledge six cases of large tumors producing hypoglycemia have been reported. So far as we have been able to determine, none of these functioning neoplasms possessed the histologic features typical of islet-cell tumor. Arkless[1] reported the occurrence of rhabdomyofibroma of the diaphragm, hypoglycemia, and retroperitoneal sarcoma in one patient. Initially a large tumor diagnosed as a rhabdomyofibroma weighing 2000 gm. was removed from the left diaphragm. Seven years later the patient returned with typical attacks of hypoglycemia, proved by blood sugar levels of 20 and 30 mg. per 100 ml. At autopsy a large neoplasm weighing 2700 gm. was found extending both above and below the diaphragm. Microscopic study of the second tumor revealed it to be comprised of small spindleshaped cells; no mitotic figures were seen. Hines[2] reported a patient with hypoglycemia due to a retroperitoneal sarcoma. Attacks of hypoglycemia proved by blood sugar levels of 30 and 26 mg. per 100 ml. were relieved by removal of a very large tumor originating in the right kidney area. Two years later the patient noted a recurrence of hypoglycemic attacks; the blood sugar content was 35 mg. per 100 ml. Shortly thereafter the patient died, and the autopsy revealed extensive metastases to the liver. Microscopic study of the original tumor revealed medium-sized, round, and polyhedral cells with granular cytoplasm and large vesicular nuclei resembling lipoblasts. Mitotic figures were also noted. The tumor was diagnosed by the pathologist as liposarcoma. However, it is possible that this neoplasm was related to the following type of adrenal growths.

Four patients have been reported as having an adrenal tumor associated with hypoglycemia. Three of these tumors reported by Anderson[3], Lawrence[4], and Broster and Patterson[5] appeared to arise in the adrenal cortex, and microscopically the cells in the tumors were similar to those seen in adrenal cortical carcinoma. The patient reported by Lawrence, in addition, had features suggestive of Cushing's syndrome, and that reported by Broster and Patterson had marked virilism. The hypoglycemia appeared to be due not to adrenal failure but rather to some substance secreted by the tumor. The hypoglycemic episodes were severe[3,4,5], and in the latter two cases[4, 5] were confirmed by low blood sugars.

A fourth case reported by Staffieri, Cames and Cid[6] was more helpful, since the pathologic findings were described in detail and illustrated. Their patient had

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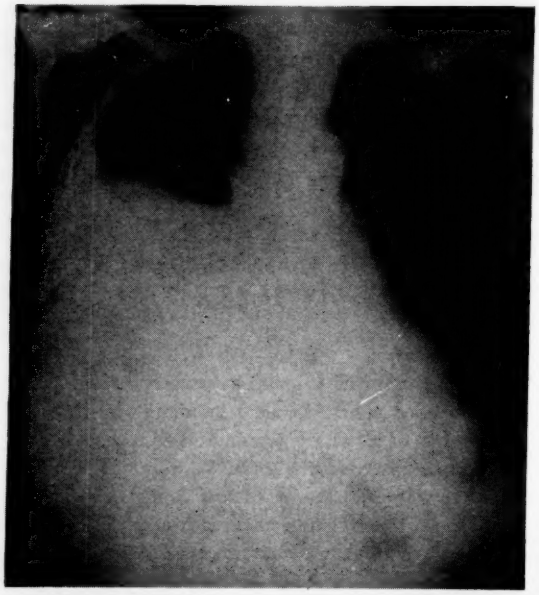
severe hypoglycemic attacks proved by blood sugar values of less than 30 mg. per 100 ml., a diffusely enlarged goiter, bilateral gynecomastia, and hepatosplenomegaly. The removal of a large tumor the size of a grapefruit (20 by 9 by 11 cm.) from the area of the right kidney resulted in complete relief of the hypoglycemic attacks and disappearance of the gynecomastia and other abnormal physical findings. Microscopic examination of the tumor revealed three types of cells. The authors state that the presence of round and spindle-shaped cells with and without reticulum suggested that this tumor might be a sarcoma, but careful study of the dense areas and the cavities filled with substance in their midst showed the epithelial nature of the cells. A third type of cell was a large polyhedral or spheroid cell whose cytoplasm was composed of vacuoles containing lipid, having some similarity to cells found in the normal adrenal cortex. This case differs from our cases in that this third type of cell was present and possibly was responsible for the gynecomastia by the secretion of estrogen-like substance.

CASE REPORTS

Case 1. A 68-year-old woman was seen by one of us (J.S.H.) in March 1952 at the Lexington Clinic, Lexington, Kentucky. For two years she had noticed the presence of a persistent, progressively more severe, nonproductive cough. In the few months prior to entry she had experienced increasing dyspnea with exertion, as well as anorexia and a weight loss of 10 pounds. During the last three to four months she had also noted increasingly severe and frequent episodes of mental con fusion and profuse sweating in the early morning, reduced by eating breakfast.

Physical examination revealed a flat percussion sound and an absence of breath sounds over the lower two-thirds of the right chest. The liver edge was palpable approximately 3 cm. below the right costal margin. There was moderate pedal edema.

A blood sample obtained during an episode of mental confusion showed a blood sugar content of 34 mg. per 100 ml. The symptoms were relieved promptly by the intravenous administration of glucose solution. A preoperative glucose-tolerance test revealed a fasting blood sugar of 45 mg.; one hour, 182 mg.; two hours, 193 mg.; three hours, 113 mg.; and four hours, 41 mg. per 100 ml. The serum albumin was 3.3 gm. and the serum globulin, 1.7 gm. per 100 ml. The thymol turbidity and cephalin flocculation tests were normal. A roentgenogram of the chest showed a large area of homogeneous density over the lower two-thirds on the right side (Figure 1). Three thoracenteses performed on the right chest removed a total of 1600 ml. of blood-tinged fluid. Micro-



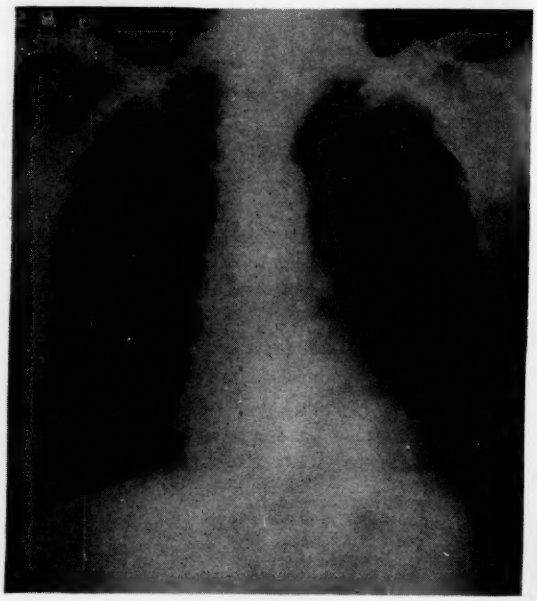


FIGURE 1. (Case 1) Roentgenogram of the chest. (a, top) Pre-operative. The large tumor mass is obscured by the pleural effusion. (b, bottom) Postoperative. Pleural thickening and absence of a rib are the only positive findings. The lung has completely re-expanded.

scopic examination of this fluid revealed numerous lymphocytes, granulocytes, and an occasional large atypical cell, believed to be evidence of malignancy.

A very large tumor, attached to the diaphragm and lower lobe of the right lung, was removed by Dr. Richard Crutcher, Lexington, Kentucky. The postoperative course was uneventful. The patient was relieved of her cough, dyspnea, and episodes of profuse sweating and mental confusion. A postoperative glucose tolerance test showed a fasting blood sugar of 69 mg.; one hour, 124 mg.; two hours, 118 mg.; three hours, 55 mg.; four hours, 60 mg.; and five hours, 73 mg. per 100 ml. The postoperative chest X ray was normal. In February 1954, 23 months after the operation, the patient had had no recurrence of either hypoglycemic symptoms or neoplasm.

Case 2. A 70-year-old man was first seen at the Cleveland Clinic in April 1953. Approximately one year previously he had noticed episodes of blurred vision, weakness, tremor, mental confusion, and more recently coma, relieved by glucose. On one occasion he had a transient quadriplegia and on another a left hemiplegia, both of which were relieved by glucose. He had also noticed increasing distress in the abdomen, due to distention, and mild dyspnea on forward bending. The hypoglycemic symptoms were most likely to occur before breakfast, but would also appear two to three hours after meals. Despite the fact that this patient had been placed on a program of frequent feedings, the attacks were becoming more frequent and more severe. He had gained 25 pounds during the previous year.

Physical examination revealed a large nodular mass that occupied the upper abdomen and produced considerable distention. After a five-hour fast in the hospital, the patient developed mental confusion and maniacal behavior; these symptoms were promptly relieved by intravenous glucose. The blood sugar content of a blood sample drawn during the espisode was 25 mg. per 100 ml. Another fasting blood sugar taken at another time was 27 mg. per 100 ml.

An exploratory laparotomy performed by one of us (G.C.) exposed a very large nodular tumor occupying the entire upper abdomen. There were numerous large vessels on the surface. Pressure atrophy of the left lobe of the liver was marked, but no hepatic metastases were noted. The tumor was encapsulated and attached posteriorly in the region of the pancreas, but there was no apparent invasion of surrounding structures. The neoplasm was carefully enucleated intact within its capsule except posteriorly where due to the size of the tumor the lines of cleavage had to be followed blindly by manual dissection. At the termination of the procedure it was still difficult to state positively where the tumor originated or whether it had been completely removed.

Postoperatively the patient developed a mild transient hyperglycemia that persisted for several days and then disappeared. There was no elevation of the serum amylase postoperatively. In February 1954, 10 months after the operation, the patient reported that he had had no recurrence of either his hypoglycemic symptoms or tumor. His fasting blood sugar was 103 mg. per 100 ml. at this time.

PATHOLOGIC FEATURES

In Case 1 the ablated tumor weighed 2440 gm. (5.4 lb.). It measured 24 by 18 by 17 cm. and was apparently encapsulated. Protruding from the surface were a number of tumor masses, measuring up to 6 cm. in diameter. Most of these were either pedunculated or lobulated. The smaller masses were soft, while those of larger size cut with considerable resistance. The cut surface was pale gray and irregularly whorled.

The surgical specimen of Case 2 was a large tumor mass, irregular in shape, measuring 21 by 16 by 15 cm. and weighing 4720 gm. (10.4 lb.). The external surface was in part covered by a thin translucent capsule and in part had a slightly shaggy appearance. It was made up of irregularly shaped lobules, varying in size from 0.5 to 10.0 cm. in diameter. The cut surface presented a variegated appearance (Figure 2). In some

FIGURE 2. (Case 2) Gross surgical specimen. The soft gray areas occurred in the inferior portion of the specimen.

areas there was marked whorling of tough gray-white septa, separating a slightly softer, neoplastic tissue, forming a pattern similar to that of a leiomyoma. Central degenerative cysts from 0.3 to 2.0 cm. in diameter were present. In other nodules the tumor tissue was homogeneous, gray, soft and friable.

In many respects these two neoplasms were histologically similar. In the first case the tumor was mostly formed of uniform, small spindle cells with rather sparse cytoplasm. The nuclei were oval with finely divided chromatin. The spindle cells were arranged in sheets and interlacing bundles (Figure 3a). In other areas, similar-sized, small, round to oval cells formed the predominant cellular flora (Figure 3b). The latter areas contained a few empty cystic spaces around which the cells were arranged. Frequent mitoses could be found in all parts of the tumor.

We were able to study the second case much more extensively and again found two merging components. The firm, white areas seen grossly were formed by small spindle cells with long cytoplasmic processes, arranged in sheets and interlacing bands (Figure 4a). Sections from the soft gray areas revealed a predominance of prismatic cells with only a faint rim of cytoplasm. They were arranged in sheets and nests, occasionally forming the wall of minute cystic-like spaces (Figure 4b). Mitoses were found in both areas.

Special staining technics provided even more contrast between tissues from the two areas. The stains used were Masson's trichrome, Mallory's phosphotungstic acid hematoxylin (PTAH), McManus' modification of periodic acid Schiff reaction (PAS), Gomori's chromalum hematoxylin phloxine, and Wilder's reticulin. In the firm areas, the cytoplasm of the cells stained green with the Masson stain; delicate fibrils similar to fibroglia were noted in the PTAH-stained section. The PAS and Gomori stains were without significance, but the reticulin stain revealed numerous coarse intercellular fibers (Figure 4c). A few spindle cells in the soft areas of the tissue were similar to those seen in the firm portion, but the reticulin was much more sparse and occurred only in short blocks (Figure 4d). The majority of the cells were round or prismatic and formed no fibrils (Figure 5.) An occasional cell, containing blue granules similar to those of beta cells, was present in sections stained with the Gomori stain.

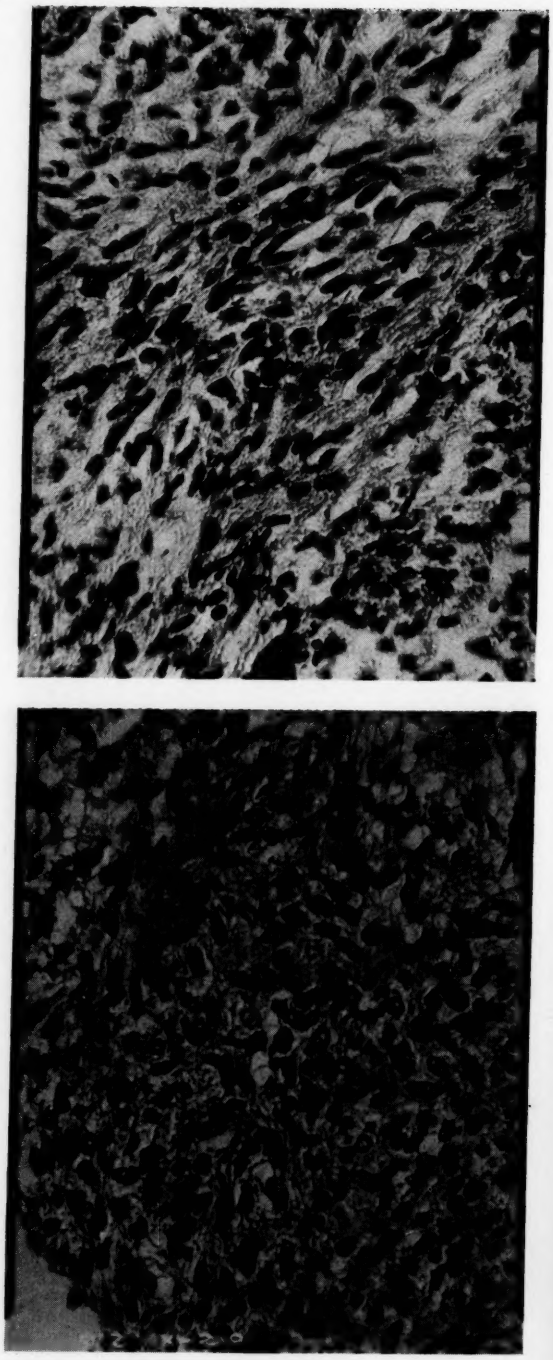


FIGURE 3. (Case 1) (a, top) Predominance of slender spindle cells. (b, bottom) Round and oval cellular forms. A few small spaces are present. Hematoxylin and eosin. X510.

COMMENT

It is our belief that these neoplasms are actually atypical, functioning islet-cell tumors of low-grade

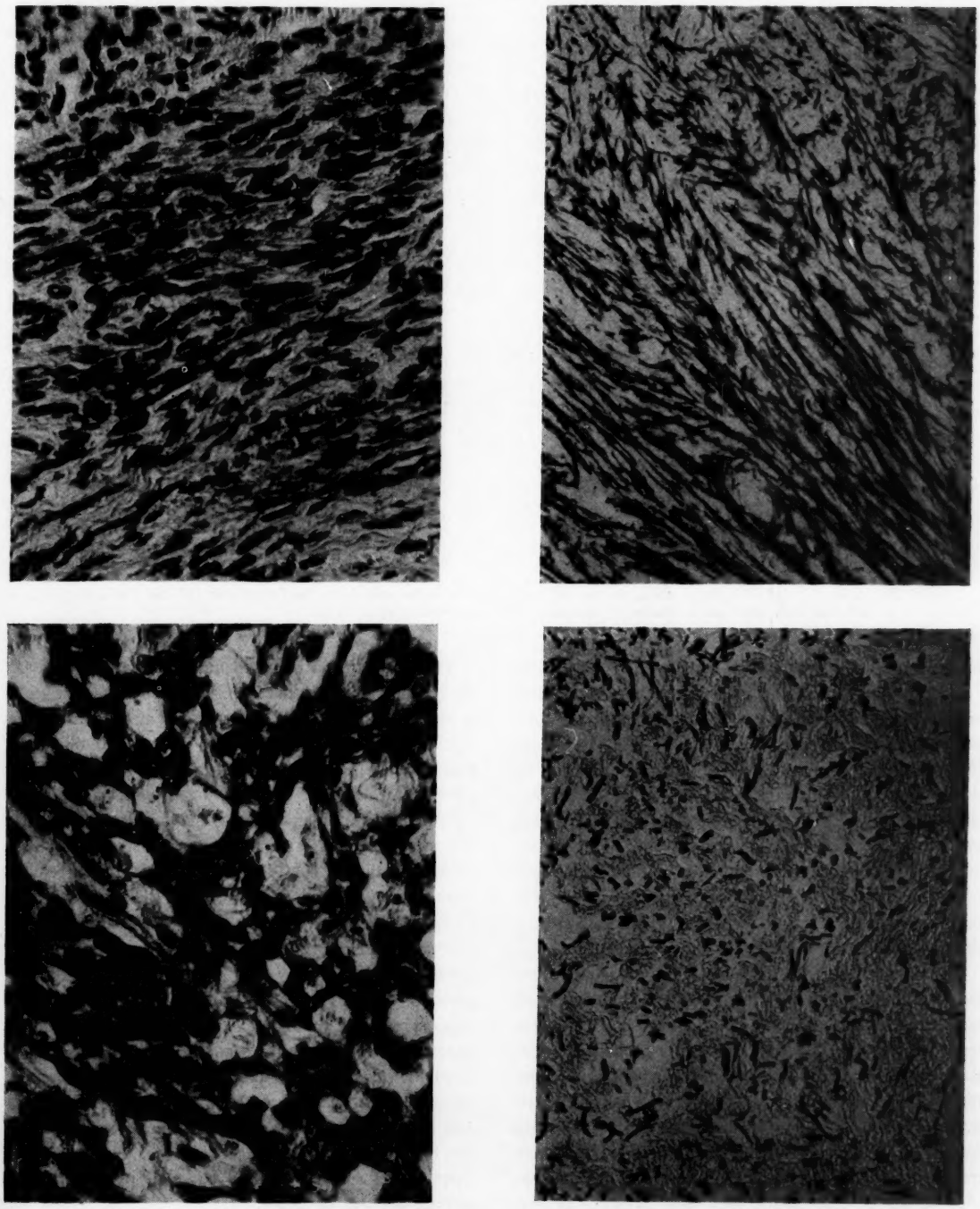


FIGURE 4. (Case 2) (a, top left) Cytology of the firm areas. Hematoxylin-eosin-methylene blue. (b, top right) Reticulin stain of (a) demonstrating the large amount of intercellular reticulin present. (c, bottom left) The soft gray areas were composed of these round cells. Small spaces are prominent in this region. Hematoxylin-eosin-methylene blue. (d, bottom right) Reticulin stain outlines coarse, less numerous reticulin strands in (c). X510.

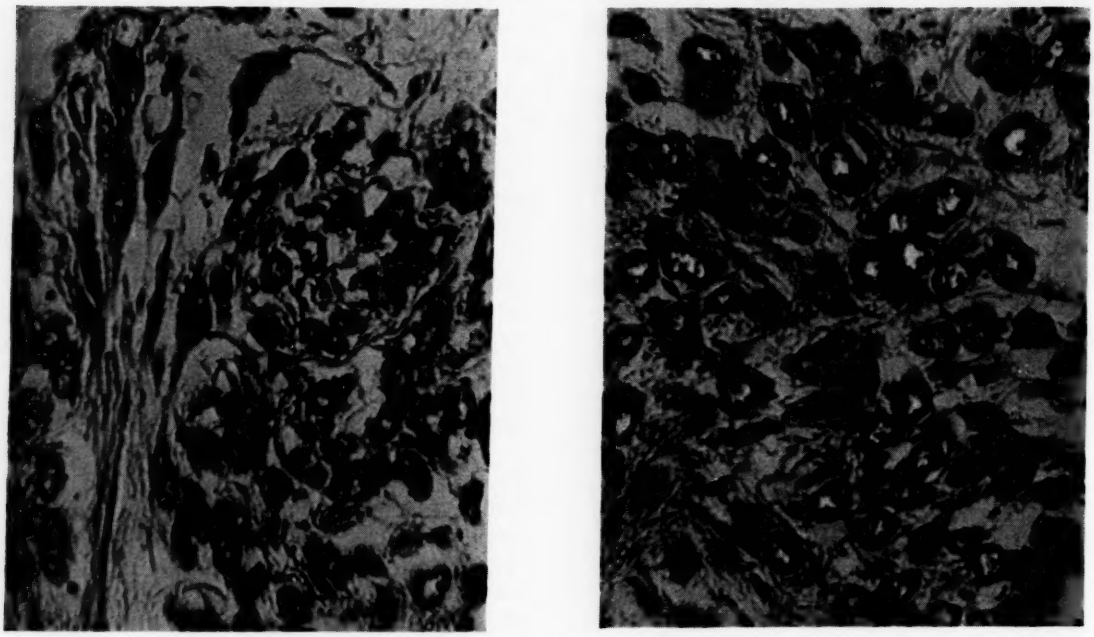


FIGURE 5. (Case 2) (a) Fibrillary processes can be seen in the spindle cells from the firm areas. (b) No fibrils are present and the cells are round. Mallory's phosphotungstic acid hematoxylin. X1050.

malignancy masquerading as sarcoma-like neoplasms.

Despite the fact that insulin assays were not done, we believe that the diagnosis of insulin-producing neoplasm is adequately justified by round cells resembling beta cells, the demonstration of blue granules in an occasional round cell in the tumor of the second patient, and, most importantly, the complete relief of organic hypoglycemia by extirpation of the tumor. The presence of the blue beta granules in an occasional round cell of the second patient's tumor suggests that the insulin may have been secreted by these round cells rather than by the spindle cells.

On the basis of the available evidence, it is our opinion that these tumors are probably low-grade islet-cell carcinomas. Their relatively rapid growth and large size favor malignancy. The spindle cells are probably epithelial cells and most likely represent a transformation from the epithelial-like round cells. That this spindle characteristic is usually, but not necessarily, a malignant feature is evidenced by its occurrence in malignant spindle-cell tumors arising from other epithelial tissues, such as the thyroid and kidney. The presence of frequent mitoses in these spindle cells is also more suggestive of a malignant transformation than it is of a benign process.

The most convincing evidence that these tumors are malignant is not demonstrated as yet by our cases, but is substantiated by the presence of metastases to the liver in the patient reported by Hines[2], and the probable local recurrence of the tumor in the patient reported by Arkless[1]. In addition, Dockerty[7], who reviewed our microscopic sections, has informed us that one such case with a sarcomatous appearance has been studied at the Mayo Clinic. In this patient, metastases were demonstrated in the liver and the patient is still living four years after the initial abdominal exploration.

That the degree of malignancy of these tumors is low grade is evidenced by the observation that our two patients have shown no evidence of recurrence of either hypoglycemia or tumor 23 and 10 months, respectively, postoperatively. Also, the patient reported by Arkless lived for seven years before the tumor recurred locally. Hines' patient had a recurrence of the hypoglycemia and tumor with metastases to the liver two years after the original tumor had been removed. Thus, the ultimate prognoses in our two patients, particularly the second, are still in doubt.

The large size of these tumors was most unusual, as contrasted with the typical islet-cell tumor. In both of our patients, the tumors were large enough to cause

local symptoms. These tumors and those reported by Arkless[1], Hines[2], and Staffieri, Cames, and Cid[6] were far larger than any ordinary islet-cell tumor previously mentioned in the literature. Brunschwig[8] reported that he had removed a nonfunctioning islet-cell adenoma weighing 673 gm., the largest we could find recorded.

The varied locations of these neoplasms were also unusual features. In our first patient, the tumor was located in the right thoracic cavity. The tumor in the patient reported by Arkless was originally located in the chest above the left diaphragm, but recurred locally and extended through the previous operative defect. The tumor in the patient reported by Hines was located in the retroperitoneal space adjacent to the right kidney. The tumor in the patient reported by Staffieri, Cames, and Cid originated in the retroperitoneal area adjacent to the right kidney. Our second patient had a tumor located adjacent to or originating from the pancreas in the retroperitoneal area. The tumor studied by Dockerty occurred in the pancreas.

It is apparent that this type of neoplasm is more likely to originate outside of the pancreas, in contrast to the usual islet-cell adenoma or carcinoma. Barbosa, Dockerty and Waugh[9] in a review of the literature found

TABLE 1

Summary of clinical features and pathologic findings in five cases of unusual, large, insulin-producing neoplasms simulating sarcoma

Case	Clinical Findings	Initial Diagnosis	Location of Tumor	Weight and Size of Tumor	Clinical Result	Microscopic Finding
Case 1	Hypoglycemic attacks 4 mo. Blood sugar 34 and 45 mg.	Neurofibrosarcoma or mesothelioma	Right thorax	2440 gm.; 24x 18x17 cm.	No recurrence of hypoglycemia or tumor 23 mo. postoperatively	Round cells without fibrils and spindle cells with cytoplasmic fibrils
Case 2	Hypoglycemic attacks 1 yr. Blood sugar 27 and 25 mg.	Fibrosarcoma	Retroperitoneal and pancreatic area	4720 gm.; 21x 16x15 cm.	No recurrence of hypoglycemia or tumor 10 mo. postoperatively	Same as Case 1 except blue beta granules in cytoplasm of occasional round cell
Arkless[1]	No hypoglycemia produced by first tumor, but present with second. Blood sugar 30 and 20 mg.	Rhabdomyofibroma; retroperitoneal sarcoma	Left thorax; retroperitoneal area below left diaphragm	First tumor: 2000 gm.; 14x22x12 cm. Second tumor: 2700 gm. 20x12x12 cm.	Local recurrence 7 yr. with death due to hypoglycemia	First: Predominant dense fibrous tissue. Second: Spindle-shaped cells
Hines[2]	Typical hypoglycemic attacks for 10 mo. Blood sugar 30 and 26 mg.	Liposarcoma	Retroperitoneal in right kidney area	Grapefruit size	Disappearance of hypoglycemia for 2 yr. until recurrence of tumor with metastases to liver and recurrent hypoglycemia	Medium-sized round and polyhedral cells
Staffieri et al[6]	Two mo. history of hypoglycemic attacks. Blood sugar 24 mg.	Corticoadrenal tumor	Retroperitoneal in right kidney area	Grapefruit size; 20x9x11 cm.	Disappearance of hypoglycemia after extirpation of tumor	Round and spindle cells with and without reticulum. Large polyhedral cell composed of vacuoles of lipoid in cytoplasm

only six cases of ordinary functioning islet-cell neoplasm originating from ectopic pancreatic tissue. All occurred in the upper abdomen and were small tumors. Whether these spindle-cell tumors originate from ectopic pancreatic islet tissue or from a more primitive type of tissue is probably only interesting speculation on the basis of available evidence.

Numerous features of some[2, 6] of the neoplasms summarized in Table 1 and the ones[3,4,5] having the uniform appearance of adrenocortical neoplasms are difficult to comprehend. Hypoglycemia relieved by the removal of a tumor has been considered to be valid evidence of the neoplasm's capacity to secrete insulin. We can understand the ability of tumor cells to imitate other cellular forms and still retain functional capabilities as evidenced in our two cases. However, the occurrence of vacuolated round cells, cells containing lipid, and finally the association of adrenocortical neoplasms producing hypoglycemia in addition to gynecomastia, and features suggestive of Cushing's syndrome and virilism form a complex endocrinologic problem not clearly understood by us at the present time, particularly since the hypoglycemia may be relieved by removal of the tumor. It is possible that in some such instances the tumors[2, 6] were composed of mixtures of islet-cell tissue and adrenocortical tissues. In others[3,4,5] in which the appearance of the cells resembled adrenocortical cells alone it is more difficult to explain the cause of the hypoglycemia, especially since adrenocortical tumors are more likely to produce hyperglycemia.

SUMMARY

The clinical features and pathologic findings of two cases of what are believed to be large, unusual, functioning islet-cell neoplasms are described. These neoplasms are unique in that they are composed of round and spindle-shaped cells, thus being quite different from ordinary islet-cell neoplasms. Their large size and unusual locations are further distinguishing features. Evidence is presented indicating that these neoplasms are probably insulin-producing, low-grade carcinomas composed of spindle-type islet cells.

ACKNOWLEDGMENT

We wish to express our appreciation to the Lexington Clinic, Lexington, Kentucky, for permitting us to present Case 1.

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ABSTRACTS

Abbis, J. W.; and Dorph, Marvin H. (*Memorial Hosp. Wilmington, Del.*): A CASE OF HEMOCHROMATOSIS (BRONZE DIABETES) IN A FEMALE. Delaware M. J. 25:292-95, October 1953.

Hemachromatosis is a disease characterized by the following triad of symptoms: pigmentation of the skin, cirrhosis of the liver, and diabetes. It is a comparatively rare disease; it is more common in males than females, and up to the year 1950, only 13 cases had been recorded in women. It is a disease of later life, the majority of cases occurring after the age of 50. No case has been described in a patient below the age of 20 years. The case described here is of unusual interest in that the patient was a female of the comparatively young age of 40 years.

The etiology of this disease remains obscure. Some years ago Mallory's theory of copper intoxication based on animal experiments proved popular, but this has now been generally discarded. It would seem that in some way the intracellular iron physiology is upset, but this is mere speculation. Attempts to produce hemochromatosis in animals by continuous intravenous administration of iron have proved inconclusive, but it is significant that in recent years cases of apparent hemochromatosis have occurred in patients who have received multiple blood transfusions over a period of years.

Anderson, Robert J. (*U. S. Public Health Service, Washington, D. C.*): NUTRITION AND THE OBESITY PROBLEM. Connecticut Med. J. 17:814-18, October 1953.

Obesity is a major public and personal health problem because of its apparent connection with specific diseases and with a shortened span of life. In diabetes, the influence of obesity is especially marked. The mortality among men with diabetes who are overweight is more than 3 times that among men of normal weight with diabetes. Obesity is considered to be the most important precipitating cause of diabetes. The need for insulin increases markedly with increased body weight.

The author believes that health departments should have an interest in weight control. They are already bringing other nutrition programs to the people. Their patient education work in diabetes and heart disease is a good example. The prenatal and well baby clinics and the care of persons in institutions are other health department activities which place a considerable emphasis on nutrition. Thus, a weight control program would not be too far outside a health department's present scope.

Bachrach, William H. (*Veterans Administration Center, Los Angeles, Calif., and the Univ. of Southern Calif., Dept. of Physiol., Sch. of Med., Los Angeles, Calif.*): ACTION OF INSULIN HYPOGLYCEMIA ON MOTOR AND SECRETORY FUNCTIONS OF THE DIGESTIVE TRACT. Physiol. Rev. 33:566-92, October 1953.

The author reviews the effect of hypoglycemia on the motor and secretary functions of the digestive tract. The existing evidence indicates that in dog and man, hypoglycemia augments those functions which are under the influence of the vagus nerves by stimulating vagal centers somewhere in the brain. Further investigation is required to establish the full scope of the hypoglycemic effect and to clarify the mechanisms concerned.

Bartlett, G. R.; and Marlow, A. A. (*La Jolla, Calif.*): ERYTHROCYTE CARBOHYDRATE METABOLISM. I. THE FLOW OF C^{14}-GLUCOSE CARBON INTO LACTIC ACID, CARBON DIOXIDE, CELL POLYMERS, AND CARBOHYDRATE INTERMEDIATE POOL. J. Lab. & Clin. Med. 42:178-87, August 1953.

Human red blood cells were incubated with C^{14}-labeled glucose for 4 hours at 38°C. They were then fractionated to determine the pathways of metabolism and the nature of the cell permanent pool of carbohydrate intermediates. Although lactic acid was formed equivalent in quantity to the glucose used, the time of incubation was such that only 50 per cent of the lactic acid carbon was derived from glucose, the remainder coming from the nonlabeled, carbohydrate storage mixture of the cell, which, in turn, was replaced by labeled carbons from glucose. This pool of tagged metabolic intermediates amounted to 20 mg. of carbon per 100 ml. of cells, approximately 15 per cent of the total trichloroacetic acid soluble carbon and about 0.1 per cent of the total cell carbon. The trichloroacetic (TCA) soluble mixture was divided into five fractions as a preliminary to analysis and isolation of the individual compounds and the carbon content and specific activity of each determined. Three fourths of the activity was found in the barium insolubles which contained about one fourth of the TCA sol-

uble carbon. Essentially negative activity appeared in the TCA insolubles emphasizing the red cell's lack of capacity for protein or fat synthesis. Slightly less than 1 per cent of the glucose carbon went to carbon dioxide, and it was calculated that this was probably due to contaminating reticulocytes and leukocytes rather than demonstrating any real respiratory capacity of the mature red cell. The barium-insoluble, alcohol-insoluble, and alcohol-soluble fractions were assayed for glucose, lactic acid, fructose, ribose, adenine, triose, total carbon, carbon derived from metabolic glucose, total phosphorus, inorganic phosphorus, and organic phosphorus hydrolyzed at ten minutes, one hour, and three hours.

Bartlett, G. R.; and Marlow, A. A. (*La Jolla, Calif.*): ERYTHROCYTE CARBOHYDRATE METABOLISM. II. CHROMATOGRAPHIC ISOLATION OF MONOPHOSPHOGLYCERATE, DIPHOSPHOGLYCERATE, AND ADENOSINE TRIPHOSPHATE AND THEIR METABOLIC TURNOVER WITH GLUCOSE CARBON. J. Lab. & Clin. Med. *42*:188-92, August 1953.

The carbon constituents of the barium-insoluble fraction of trichloroacetic acid extracts of human erythrocytes have been isolated by ion exchange chromatography as adenine, ribose-5-phosphate, 3-monophosphoglycerate, and 2,3-diphosphoglycerate. The phosphoglycerates showed a high turnover rate with glucose carbon, adenine none, and ribose-5-phosphate possibly a trace.

Becker, Bernard; Lang, Calvin A.; and Chow, Bacon F. (*John Hopkins Univ.*): VITAMIN B_{12} EXCRETION AND DIABETIC RETINOPATHY. J. Clin. Nutrition *1*:417-23, September-October 1953.

All subjects were given 50 or 65 micrograms vitamin B_{12} intramuscularly. Determinations of urinary excretions were made on specimens collected during the eight hours immediately after injection. Collection of urine for an additional 16 hours seldom yielded more than 5 per cent of that excreted in the first 8 hours, so that it was not routinely done.

Thirteen diabetics without retinopathy (no evidence of capillary aneurysms, exudates, or hemorrhages) excreted an average of 4.2 micrograms with SE $\pm$ 1.7; 22 diabetics with retinopathy excreted an average of 19 micrograms $\pm$ 2.1; and 6 healthy controls excreted an average of 9.6 micrograms $\pm$ 1.4. No significant difference was noted with age. Eleven diabetics with retinopathy were given 100 to 200 mg. testosterone cyclopentylpropionate intramuscularly every two to three weeks, and vitamin B_{12} excretion tests were made at intervals of at least four weeks. In each instance there was a significant decrease in the vitamin B_{12} excretion so that all fell to or below the normal mean of 9.6 micrograms. This would make unlikely the thesis that the difference was due to differences in renal function in the two groups. It is suggested by the observations on vitamin B_{12} excretion of cortisone-treated rats that the increased excretion of B_{12} in diabetics with retinopathy may be related to the finding of high urinary concentrations of oxysteroids related to but not identical with cortisone in such individuals as compared with the diabetics without retinopathy.

Benjamin, H. B.; Wagner, Marvin; and Zeit, Walter (*Dept. of Anat., Marquette Univ. Sch. of Med., Milwaukee, Wis.*): INTRAGASTRIC TEMPERATURE VARIATIONS IN MAN DURING HUNGER. Science *118*:160, August 7, 1953.

By means of a fluoroscopically placed thermopile in human subjects, the authors observed that the intragastric temperature fell about 1°F about thirty minutes after the onset of hunger pangs, with a return to the previous plateau on their subsidence. It is postulated that the drop in temperature is due to decreased intragastric metabolic activity because the neurovascular mechanism of the stimulated stomach produces a state of anemia of the mucous membrane in consequence of the shunting mechanism of the vascular bed when muscular contractions arrest the blood flow.

Bing, Franklin C. (*Chicago, Ill.*): PROFESSOR LAFAYETTE B. MENDEL AS A MEDICAL ESSAYIST. Yale J. Biol. & Med. *26*:139-44, November 1953.

Bing writes of Lafayette B. Mendel, the late renowned physiological chemist at Yale, as an essayist and especially as an editorial writer for the *J.A.M.A.* His early contributions to the *Dietetic and Hygienic Gazette* in 1894 included reviews on diet, foodstuff, food and animal heat, observations on phlorizin diabetes, and the relation of the venous system to the glycogenic function of the liver and diabetes. The number of his contributions was amazing, and the quality of his essays was uniformly excellent. The essays were stimulating at the time they were published, and they make informative and interesting reading today.

Bukantz, S. C.; and Klingberg, W. (*St. Louis Children's Hosp., St. Louis, Mo.*): SKIN TEST RESPONSES TO INSULIN AND SERUM ANTIHORMONAL ACTIVITY IN A CASE OF COMBINED INSULIN ALLERGY AND RESISTANCE. J. Lab. & Clin. Med. 42:791, November 1953. (Abstract from Proceedings of 25th Annual Meeting, Central Society for Clinical Research.)

A 3½-year-old diabetic child was found to be considerably resistant to insulin and concurrently showed marked local skin reactions at injection sites and a blood eosinophilia of 17 per cent. Investigation showed that the allergy to insulin was directed against a contaminant rather than the hormone, and resistance did not seem related to this contaminant. The allergen in commercial insulin was heat stable. Serum obtained at the height of resistance was found to have some antiinsulin effect in mouse convulsion tests, but this effect did not significantly exceed that of control normal or nonresistant diabetic serum.

Byers, Sanford O.; Friedman, Meyer; and Gunning, Barbara (*Harold Brunn Inst., Mount Zion Hosp., San Francisco, Calif.*): OBSERVATIONS CONCERNING THE PRODUCTION AND EXCRETION OF CHOLESTEROL IN MAMMALS. XI. THE INTESTINAL SITE OF ABSORPTION AND EXCRETION OF CHOLESTEROL. Am. J. Physiol. 175:375-79, December 1953.

The small intestine of the rat was found to be responsible for the major portion of the cholesterol excreted into the intestinal contents. The distal half of the small intestine was the only portion capable of absorbing exogenously derived cholesterol.

Campbell, James; Munroe, J. S.; Hausler, H. R.; and Davidson, I. W. F. (*Dept. of Physiol., Univ. of Toronto, Toronto, Canada*): EFFECTS OF GROWTH HORMONE IN DIABETIC DOGS. Endocrinology 53:549-63, November 1953.

Injections of purified growth hormone greatly aggravated the severity of diabetes in depancreatized dogs and in a metahypophyseal diabetic dog that were maintained on a steady dose of insulin.

In these diabetic dogs given their usual supply of insulin, the injections of growth hormone increased the plasma fibrin and the erythrocyte sedimentation rate. Leucocytosis due to marked increases in neutrophil granulocytes and lesser increases in band cells occurred. Massive deposition of fat occurred in the liver, and the content of fat-free solids increased. The lipid content and the fat-free solids of the kidney also increased. Severe fatty degeneration of the heart occurred in the metahypophyseal diabetic dog given growth hormone.

Evidence from depancreatized dogs deprived of insulin indicates that the increase in liver and kidney fat of the dogs given growth hormone may be due, in part at least, to a relative deficiency of insulin. Withdrawal of insulin from depancreatized dogs was followed by neutrophilia, with a relatively small effect on stab cells. In these dogs, the plasma fibrin levels and the sedimentation rate were high and rather variable but were not altered significantly by lack of insulin. Evidence is given which suggests that the growth hormone creates an increased metabolic demand for insulin and increases, at an early stage of its effects, the rate of secretion of insulin by the pancreas.

Injections of purified growth hormone (D21P) in doses of 0.25 to 0.5 mg. per kilo per day for 3 to 4 days greatly aggravated the severity of the diabetes in depancreatized dogs and in a metahypophyseal diabetic dog maintained on constant insulin dosage. Evidence is presented that the growth hormone creates an increased metabolic need for insulin and increases in an early stage of its effects the rate of secretion of insulin by the pancreas.

In insulin-treated depancreatized dogs, growth hormone increased the plasma fibrin and sedimentation rate, the white blood count, and the content of fat-free solids and produced a massive deposition of fat in the liver.

Cohen, E. M.; Kok-Van Alphen, C. C. (*Pharmacological Lab., Univ. of Leiden, Dept. of Ophthalmology, Leiden Univ. Hosp.*): INSULIN AGAINST ALLOXAN DIABETIC CATARACTS IN RATS. Acta physiologica et pharmacologica neerlandica 3:81-84, October 1953.

Seven out of eight well-developed cataracts in alloxan-diabetic rats underwent a marked regression after an insulin treatment which diminished the daily output of urine and urine sugar. No improvement was observed in untreated controls.

Craig, J. W.; Miller, Max; Woodard, Hiram, Jr. and Drucker, W. R. (*Sch. of Med., Western Reserve Univ., Cleveland, Ohio*): STUDIES OF FRUCTOSE METABOLISM

IN INSULIN RESISTANT DIABETES. Am. J. Med. *14*: 500, April 1953. [Abstract of a paper presented at the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 4, 1952.]

Insulin was withdrawn in a patient requiring 1,100 units of insulin daily, and 100 gm. of fructose were given intravenously each morning for nine days. Blood fructose disappearance curves, blood pyruvate and phosphorous levels, and urinary fructose excretion were similar to those found in normal subjects and were unchanged after nine days. Similar studies following nine days of oral administration by either route also revealed no loss of fructose tolerance. Fructose was better utilized than glucose administered by either route. Blood fructose curves were not altered by insulin. For two weeks the patient received a constant diet to which 138 gm. of either fructose or glucose was added on alternate days. When the sugars were thus distributed in the diet, the twenty-four hour urinary excretion of hexose did not demonstrate any striking advantage of fructose over glucose.

Curran, George L. (*Res. Lab., The Mary Imogene Bassett Hosp., Cooperstown, N. Y.*): EFFECT OF *p*H ON CHOLESTEROL SYNTHESIS BY SURVIVING RAT LIVER. J. Biol. Chem. 200:17-21, January 1953.

The rate of cholesterol synthesis by surviving rat liver at *p*H 6.0 to 7.2 was found to be markedly greater than at *p*H 7.2 to 7.4. The optional *p*H range for cholesterol synthesis in vitro was 6.2 to 6.8. In view of the magnitude of the increase in cholesterol synthesis caused by a drop in *p*H to 6.5, the author advances the hypothesis that reduction in intracellular *p*H may play a role in the hypercholesterolemia found in diseases associated with disturbances in acid-base balance, such as diabetes mellitus.

Desmond, Murdina M. (*Dept. of Pediat., Baylor Univ. Coll. of Med., Houston, Texas*): OBSERVATIONS RELATED TO NEONATAL HYPOGLYCEMIA. J. Pediat. *43*: 253-62, September 1953.

Premature as well as full-term infants respond to an epinephrine injection with a rise in blood glucose. In the first days of life, the increase in blood glucose is less and the rise less rapid than the rise at the end of the first week of life.

The intravenous glucose tolerance curves of both premature and full-term infants are essentially within normal limits. Both groups demonstrate an ability to recover from the low levels reached in the descending limb of the curve. Blood glycogen levels in the newborn period are within the normal adult range.

Within the limits of this study, no relation could be demonstrated between the eosinopenic and glycemic response of the newborn infant to epinephrine injection. Theories of the origin of the phenomenon of neonatal hypoglycemia are discussed.

Drury, M. I. (*Mater Misericordiae Hospital, Dublin*): THE NEW "LENTE" INSULINS. J. Irish M. A. 33:96-97, October 1953.

Experiences with the sulfonamide compounds and the antibiotic drugs have led many to view with dismay the introduction of new preparations of drugs in common use. It is to be expected, therefore, that the welcome for a new insulin compound will be cool unless it can be shown that it has distinct advantages over existing preparations. The manufacturers of lente insulin claim that it possesses such advantages, and reports of clinical trials by Hallas-Møller and by Laurence and Oakley substantiate that claim. This brief communication presents a summary of the results obtained in the treatment of 14 patients with this preparation.

In the 14 cases under review, good control was achieved in 9 by means of a single daily injection of lente insulin. Five of these nine patients would be classed as severe cases. In the remaining five patients (4 severe), control with lente insulin alone was not quite satisfactory. The addition of semi-lente (having quick action) in two cases and of ultra-lente (having prolonged action) in three cases resulted in satisfactory control. This preliminary trial suggests that the "lente insulins" are a decided advance on available preparations.

Drury, M. I. (*National Maternity and Coombe Lying-In Hospitals, Dublin*): MANAGEMENT OF THE PREGNANT DIABETIC. J. Irish M. A. 33:91-95, October 1953.

A high incidence of fetal loss is a feature of pregnancy complicated by diabetes. The prospects of fetal survival are improved by rigorous control of the diabetic state from an early stage of the pregnancy, by induction of

labor or cesarean section at 36 weeks, and by skilled pediatric attention. To achieve this, all doctors who have married diabetics under their care should impress upon these women the importance of reporting as early as possible in their pregnancies. Patients should be referred to a maternity hospital as soon as the diagnosis of pregnancy is confirmed. There is no indication for "therapeutic" abortion in the diabetic woman.

Editorial (*New York City*): In Vitro STUDIES OF INTESTINAL CARBOHYDRATE ABSORPTION. Nutrition Rev. *11*: 280-81, September 1953.

Using segments of guinea-pig intestine, a separate perfusion system for the intestinal lumen, the external bathing medium, and a means for sampling the solutions without interrupting the operation of the system, the authors found the absorption of sugars to be galactose, 100; glucose, 100; fructose, 50; sorbose, 37. They also found the latter to be the result of passive diffusion. The transformation of fructose to glucose during absorption was studied, and the reducing activity in the outer fluid was found to be much greater than could be accounted for by the fructose present as such. Fructose appeared in the outer solution at about the same rate as did sorbose, and they interpreted the results to mean that some fructose is transformed into glucose in passage through the intestinal wall. Phosphate was not necessary in the perfusion fluids for the absorption of the sugars, but it was possible to relate the sugar absorption to respiratory activity. Cyanide, ozide, fluoroacetate, malonate, chloretone, and especially 2, 4-dinitrophenol were effective in inhibiting glucose absorption.

Engel, Frank L.; and Hewson, Kathleen (*Depts. of Med. and Physiol., Duke Univ., Durham, N.C.*): FATTY ACID AND KETONE METABOLISM DURING HEMORRHAGE AND SHOCK IN THE RAT. Proc. Soc. Exper. Biol. & Med. *83*:608-11, July, 1953.

Sublethal hemorrhage in the normal fasted rat without a significant rise in plasma amino nitrogen is followed by a prompt suppression of fasting ketosis but is without effect on the increase in blood ketones consequent to a 30-minute intravenous infusion of sodium octanoate. Hemorrhagic shock with rising plasma amino nitrogen levels is associated with a significant and progressive hypoketonemia and an inhibition of the rise in blood ketones ordinarily seen after sodium octanoate infusion. Adrenalectomized rats exhibit the same decline in blood ketone levels during hemorrhage and shock as do normal rats. The authors suggest that ketone production from fatty acids in the liver may be suppressed during shock.

Engleson, Gunnar (*Allhelgona Kyrkogata 10, Lund, Sweden*): INSULIN NOVO LENTE IN ONE DAILY INJECTION IN DIABETES IN CHILDREN. Nord. Med. 50:1012, July 16, 1953.

An account is given of experience with some new insulins (insulin semi-lente, lente, and ultra-lente) in the treatment of diabetes in children. All the patients had severe diabetes. Some were "brittle" diabetics, and several had to take two insulin injections daily before starting the treatment. All twenty-two patients were improved. Nineteen of them showed a very good adjustment. Although no statistically conclusive results can be adduced because of the small series, the investigation has shown that there is a good reason to account these insulins an equally good value in the treatment of juvenile diabetes as in adults.

Euler, von, U. S.; and Luft, R. (*Serafimerlasarettet, Stockholm K, Fysiologiska Institutionen, Karolinska Institutet, Stockholm, Sweden*): THE EFFECT OF INSULIN ON THE EXCRETION OF ADRENALINE AND NORADRENALINE IN HEALTHY SUBJECTS AND IN CASES OF ACROMEGALY AND POSTURAL HYPOTENSION. Nord. Med. *49*:56, January 9, 1953.

A tenfold increase in the excretion of adrenaline in the urine after intravenous injection of 0.1 international unit of insulin per kg. of body weight in 10 healthy young subjects indicated an increased adrenaline secretion. This was also borne out by the accompanying circulatory symptoms. In acromegalic patients the usual symptoms accompanying hypoglycemia were absent, and the extra output of adrenaline in the urine was also small or absent, indicating a disturbed response to hypoglycemia. Two cases of postural hypotension showed a very low resting output of catechol amines and a very slight increase in adrenaline output after insulin.

Foa, P. P.; Magid, E. B.; Glassman, M. D.; and Weinstein, H. R. (*Dept. of Physiol. and Pharmacol., The*

Chicago Med. Sch.): ANTERIOR PITUITARY GROWTH HORMONE (STH) AND PANCREATIC SECRETION OF GLUCAGON (HGF). Proc. Soc. Exper. Biol. & Med. *83*:758-61, August-September 1953.

Fourteen crosscirculation experiments were performed by anastomosing the pancreato-duodenal or a mesenteric vein of a donor dog with a femoral vein of a recipient dog. The intravenous injection of purified anterior pituitary growth hormone (somatotrophic hormone or STH) into a normal donor or into a donor previously treated with the same STH causes the appearance of a hyperglycemic material (glucagon) in the blood of the pancreatic but not of the mesenteric vein. This glucagon causes hyperglycemia in a normal recipient dog. In addition to decreasing insulin secretion and inhibiting peripheral utilization of glucose, STH appears to cause hyperglycemia by stimulating the secretion of glucagon by the pancreas. It is believed that these results further support the hypothesis that glucagon is a pancreatic anti-insulin hormone contributing to the maintenance of a normal blood sugar concentration.

Foreign Letters (*England*): ARTIFICIAL SWEETENERS IN FOOD. J.A.M.A. *153*:1378, December 12, 1953.

In the future only saccharin will be permitted as an artificial food sweetener (Artificial Sweeteners in Food Order, 1953). This follows a recommendation from the Medical Research Council. Saccharin is known to be harmless, but, according to the Council's Food Adulterants Committee, the use of certain other artificial sweetening agents may be dangerous to health.

Furman, R. H.; Ball, Con O. T.; Gale, Robert B.; Billings, F. Tremaine; and Meneely, George, R. (*Dept. of Med., Vanderbilt Univ. Sch. of Med., and the Res. Lab., Thayer V. A. Hosp. Nashville, Tenn.*): AN EVALUATION OF ANTICOAGULANT THERAPY IN MYOCARDIAL INFARCTION BASED ON PROGNOSTIC CATEGORIES. Am. J. Med. *14*:681-88, June 1953.

Dicumarol or dicumarol and heparin were administered during 100 episodes of acute myocardial infarction. An earlier group of 211 patients served as controls. Patients were sorted into prognostic categories according to the following criteria: (1) *Very poor risks*: (a) The attack was the patient's first; shock and diabetes or shock and azotemia were present; (b) a previous attack had occurred; shock was present, or congestive failure and diabetes and azotemia were present. (2) *Poor risks*: Shock, congestive failure, diabetes, or azotemia was present within the first week of admission. (3) *Good risks*: None of the concomitant manifestations in groups 1 and 2 was present.

Anticoagulants failed to improve the mortality in the "very poor risk" category. The mortality in the "good risk" category was very small, with or without anticoagulants. The beneficial effects of anticoagulants were most apparent in the "poor risk" group of patients and then chiefly so in those less severely ill. Such beneficial effects could not be entirely ascribed to a reduction in thromboembolic phenomena.

The need for further evaluation of anticoagulant therapy in myocardial infarction within a framework of prognostic categories is emphasized.

Gitlin, David; and Janeway, Charles A. (*Dept. of Pediat., Harvard Med. Sch., and the Children's Med. Center, Boston, Mass.*): THE DYNAMIC EQUILIBRIUM BETWEEN CIRCULATING AND EXTRAVASCULAR PLASMA PROTEINS. Science *118*:301-02, September 11, 1953.

The authors present data showing that preformed plasma protein in the extravascular pool can move rapidly into the circulation upon depletion of the specific protein in the latter compartment. Thus, the extravascular plasma protein is in dynamic equilibrium with the intravascular plasma protein; once equilibrium is established, a decrease in the mass of a specific plasma protein in one compartment results in the movement of that plasma protein to that compartment until equilibrium is again attained.

Goldner, M. G.; and Jauregui, R. H. (*Dept. of Med., Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N.Y., and the State Univ. of N.Y. Med. Center at N.Y.*): EFFECT OF ALLOXAN ON ISOLATED LIVER OF THE BULLFROG. Proc. Soc. Exper. Biol. & Med. *84*:116-20, October 1953.

Alloxan inhibits the spontaneous glycogenolysis of the perfused liver of the bullfrog. Epinephrine glycogenolysis is inhibited by alloxan if given previously or simultaneously. These experiments support the hypothesis that the hypoglycemia found early after alloxan administration is of hepatic rather than pancreatic origin.

Gowen, G. Howard (*Div. of Hosp. and Chronic Illness, Illinois Dept. of Public Health*): SCREENING FOR DIABETES. Illinois M.J. *104*:293-94, November 1953.

An exhibit on diabetes at a state fair included performance of screening tests for diabetes.

Griffiths, J. A. (*Royal Infirmary Unit, United Sheffield Hosp.*): THE EFFECTS OF GENERAL ANAESTHESIA, AND HEXAMETHONIUM, ON THE BLOOD-SUGAR IN NONDIABETIC AND DIABETIC SURGICAL PATIENTS. Quart. J. Med. *22*:405-17, October 1953.

Two cases are described of severe hypoglycemia occurring in diabetic surgical patients under light general anesthesia, during which the technique of controlled hypotension with hexamethonium bromide was employed. In the investigation of these occurrences, experiments under standard conditions gave the following results in selected nondiabetic patients under general anesthesia: (1) During superficial operations in 20 subjects, the blood sugar remained constant throughout. (2) During upper abdominal operations in 10 cases there was a maintained rise of the blood sugar level, which was statistically significant but clinically unimportant. (3) During superficial operations in 25 cases under induced hypotension with hexamethonium bromide, the blood sugar decreased after hexamethonium was given, remaining stable at this lower level. (4) In two cases hexamethonium greatly potentiated the action of parenteral insulin, causing severe hypoglycemia. Three patients with controlled diabetes showed a stable blood sugar with the standard anesthetic technique. Considerable potentiation of insulin occurred in one additional case of diabetes in which hypotension was induced with hexamethonium. Hexamethonium in the anesthetized subject masked many of the signs of hypoglycemia, even when severe. The only constant sign was a progressive tachycardia. It is concluded that controlled hypotension with hexamethonium is strongly contraindicated in diabetic patients.

Harvey, Stewart C.; and Higby, Velma (*Dept. of Pharmacol., Univ. of Utah, Coll. of Med., Salt Lake City, Utah*): A MICROCOLORIMETRIC METHOD FOR THE DETERMINATION OF GLUCOSE. Texas Rep. Biol. & Med. *11*:489-93, Fall, 1953.

A micromethod for the quantitative colorimetric estimation of glucose is described. Glucose and catechol are heated in sulfuric acid at 140-5° C. to give a red color. The method can be employed in the presence of reducing substances, which would render the usual methods inaccurate.

Haugaard, Ella S.; and Stadie, William C. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Penn.*): THE EFFECT OF HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR AND EPINEPHRINE ON FATTY ACID SYNTHESIS. J. Biol. Chem. *200*:753-57, February 1953.

The authors were able to confirm the stimulatory effect of insulin on the incorporation of acetate into liver fatty acids with a crystalline preparation of insulin. With an amorphous preparation of insulin, a decrease in fatty acid synthesis was observed. Hyperglycemic factor and epinephrine were found to depress the incorporation of acetate into fatty acids. The significance of these findings is discussed.

Hess, W. C.; and Shaffran, I. P. (*Dept. of Biological Chem., Georgetown Univ. Sch. of Med., Washington, D.C.*): EFFECT OF CORTISONE UPON FORMATION OF LIVER GLYCOGEN FROM GLYCINE. (20497) Proc. Soc. Exper. Biol. & Med. *83*:804-06, August-September 1953.

Glycine and cortisone each produce increases in liver glycogen of fasted normal rats. When given together, neither dosage (2.5 or 5 mg.) of cortisone increased the amount of glycogen formed from glycine. The authors interpret the results either that maximum utilization was occurring and no further increase could result from the action of cortisone or that the action of the adrenal cortex on nitrogen metabolism may be on protein rather than on amino acids.

Hoffman, H. L.; Jacobs, J.; and Freedlander, S. O. (*Mount Sinai Hosp., Cleveland, Ohio*): USE OF CRYSTALLINE SOYBEAN TRYPSIN INHIBITOR IN ACUTE HEMORRHAGIC PANCREATITIS IN DOGS. A. M. A. Arch. Surg. *66*:617-23, May 1953.

Experimental hemorrhagic pancreatitis was created in 91 dogs. Thirty dogs were untreated and were used as controls; the mortality rate was 50 per cent. Sixty-one dogs were treated with pure crystalline soybean trypsin inhibitor in varying dosages; the mortality rate was 50.8 per cent. Crystalline soybean trypsin inhibitor was thus

found to be ineffective in the treatment of experimental acute hemorrhagic pancreatitis in dogs under the condition of these experiments.

Ingle, D. J.; Beary, D. F.; and Purmalis, A. (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): EFFECT OF CONTINUOUS INJECTION OF EPINEPHRINE UPON THE GLYCOSURIA OF PARTIALLY DEPANCREATIZED RATS. Proc. Soc. Exper. Biol. & Med. *84*:112-14, October 1953.

Epinephrine was administered to normal and to partially depancreatized force-fed rats by continuous subcutaneous injection for periods of 3 and 4 weeks. Simultaneously the control animals were injected with saline. Increased amounts of glucose were excreted by both normal and partially depancreatized rats during the injection of epinephrine. The peak response occurred on the second day after starting the injection of epinephrine or increasing the dose. All of the animals showed adaptation to epinephrine so that the peak response was not sustained.

Ingle, D. J.; Meeks, R. C.; and Beary, D. F. (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): TIME-RESPONSE EFFECT OF CORTISONE UPON LIVER GLYCOGEN IN THE RAT. Proc. Soc. Exper. Biol. & Med. *84*:239-40, October 1953.

Male rats having an initial weight of approximately 300 gm. were given single daily injections of cortisone acetate in doses of 2, 5, and 10 mg./rat/day. At each of the 3 dosage levels, 6 to 8 rats were killed at intervals ranging from 1 to 42 days, and the amount of liver glycogen was determined in each rat. The level increased significantly, reaching a peak within 5 days, and was followed by a significant decline towards, but not reaching, normal values. The concentration of glycogen in the liver reached 9.26 per cent for the group treated with 10 mg. of cortisone for 5 days.

Ingle, D. J.; Nezamis, J. E.; and Humphrey, L. M. (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): EFFECT OF ADRENAL CORTICAL EXTRACT AND STEROIDS UPON GLUCOSE TOLERANCE OF EVISCERATED RATS. Proc. Soc. Exper. Biol. & Med. *84*:45-47, October 1953.

Eviscerated rats were each given continuous intravenous injections of 20 cc. per 24 hours of solutions containing glucose, insulin, and antibiotics with and without adrenal cortical hormones. Adrenal cortical extract caused a significant elevation of blood glucose above the average value for control animals, but cortisone and hydrocortisone were relatively ineffective.

Ingle, D. J.; Nezamis, J. E.; and Meeks, R. C. (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): EFFECT OF ADRENAL CORTICAL EXTRACT UPON WORK OUTPUT AND GLUCOSE TOLERANCE OF ADRENALECTOMIZED-EVISCERATE RAT. (20409) Proc. Soc. Exper. Biol. & Med. *83*:537-39, July 1953.

The continuous intravenous injection of adrenal cortical extract to adrenalectomized-eviscerate rats improved work output during the faradic stimulation of muscle in one hind leg. There was a concomitant elevation of blood glucose above the level of the untreated rats when the animals continued to work. When both hind legs were stimulated, muscular responsiveness was completely lost in each of the untreated rats within 6 hours, and there was an immediate rise in the level of blood glucose above the values for the treated rats which continued to work. The presence of the liver and other intra-abdominal organs is not required for an effect of adrenal cortical hormones upon muscle work. The effect of adrenal cortical extract in impairing the utilization of glucose is at least in part extrahepatic.

Jacobson, Jacob (*New York, N.Y.*): VASCULAR CHANGES IN DIABETIC AND ARTERIOLOSCLEROTIC RETINOPATHY OBTAINED BY A MODIFIED SOLUTION OF BENZYL CINNAMATE. New York J. Med. *53*:970-74, April 15, 1953.

The author treated a series of 33 cases of diabetic and arteriolosclerotic retinopathy with a modified solution of benzyl cinnamate. The cases were chosen among patients who had not been improved by previous methods of therapy and whose vision was gradually diminishing. Twenty-five cases are said to have experienced improvement of vision in various degrees. (Neither the mode, amount of drug, nor length of treatment is given.)

James, William E. S.; Wisenbaugh, Paul E.; and Shumway, Norman P. (*Cleveland, Ohio*): PAIN CAUSED BY POTASSIUM INTOXICATION IN A PATIENT WITH KIMMELSTIEL-WILSON SYNDROME. J.A.M.A. *153*:545-46, October 10, 1953.

This case report of hyperkalemia in a patient with Kimmelstiel-Wilson syndrome describes an unusual and previously unreported type of pain, described as a cramping, gnawing ache in the upper extremities, hands, and jaws, associated with potassium intoxication. The pain was controlled by administration of excess potassium. This report also illustrates the possible occurrence of hyperkalemia after excessive administration of orange juice and meat broth in treatment of insulin reactions.

Kalinowski, S. Z.; and Walker, J. Miles *(London):* DIABETIC COMA ASSOCIATED WITH LIPAEMIA AND COMPLICATED BY URAEMIA. Brit. M. J. 2:661-62, September 19, 1953.

Although many cases of lipemia associated with diabetic coma have been reported, the following case is of interest because of the marked degree of lipemia attained, with the manifestation of lipemia retinitis, and also because of the unusual feature of temporary kidney dysfunction.

In view of the appearance of the fundi, which were strongly suggestive of lipemic retinitis, the following laboratory tests were made: serum free cholesterol, 220 mg. per 100 ml.; serum ester cholesterol, 710 mg. per 100 ml.; and serum total lipoids, 7.84 per cent. The blood serum was of a whitish, opalescent, milky appearance and became solidified as it cooled to room temperature. The cerebrospinal fluid was cytologically and biochemically normal, apart from an elevated sugar fraction, but it also presented an opalescent slightly "milky" appearance.

The patient's output of urine was very small. Her blood urea steadily rose to a maximum of 180 mg. per 100 ml. nine days after admission, with gradual deterioration in her general condition. Her blood urea level persisted unchanged for the next 10 days, after which it slowly declined to normal, accompanied by an increase in urinary output, the disappearance of the hyperlipemia, a return of the renal sugar threshold to normal, and much improvement in her general condition.

Kinsell, L. W.; Balch, H. E.; and Michaels, G. D. (*Inst. for Metabolic Res. of the Highland Alameda Ct. Hosp., Oakland, Calif.*): ACCENTUATION OF HUMAN DIABETES BY "PITUITARY GROWTH HORMONE." (20458) Proc. Soc. Exper. Biol. & Med. 83:683-86, August-September 1953.

Administration of "highly purified pituitary growth hormone" to a diabetic patient, under chemically controlled conditions, resulted in increased hyperglycemia and glycosuria, in minimal increase in blood and urinary ketones, and in minimal change in the nitrogen balance. The data support the concept that the increased hyperglycemia and glycosuria are probably attributable to diminished carbohydrate utilization rather than increased neoglucogenesis.

Kirkendall, Walter M.; Sinton, David W.; and Culbertson, James W. (*Iowa City, Iowa*): THE MAXIMAL RENAL TUBULAR REABSORPTION OF FRUCTOSE IN NORMAL AND DIABETIC MAN. (Abstract from Proceedings of 25th Annual Meeting, Central Society for Clinical Research.) J. Lab. & Clin. Med. 42:827, November 1953.

Hypertonic solutions of fructose were infused in five diabetic and seven nondiabetic patients. Using arterial blood samples, relatively stationary plasma fructose levels and sodium thiosulphate as the measure of glomerular filtration rate, the maximal tubular reabsorption of fructose (Tm_f) by the kidney was calculated. Tm_f was found to vary from 40 to 130 mg./min. Saturation of all tubular reabsorptive mechanisms probably occurs at serum fructose levels under 100 mg. per cent in most normal persons. Diabetics have Tm_f values similar to normal persons, and these are not altered at increased plasma glucose levels.

Krahl, M. E. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): INCORPORATION OF C^{14} AMINO ACIDS INTO GLUTATHIONE AND PROTEIN FRACTIONS OF NORMAL AND DIABETIC RAT TISSUES. J. Biol. Chem. 200:99-109, January 1953.

Incorporation of glycine -1-C^{14} into glutathione and protein by rat liver slices was reduced in severe diabetes. Addition of glucose to the incubation medium in vitro raised incorporation toward the normal, and the further addition of insulin restored incorporation completely to normal. In the absence of added substrate, insulin alone had no effect on amino acid uptake by diabetic liver. Incorporation of glycine -1-C^{14} into a protein fraction of rat diaphragm was also reduced in diabetes. This could be raised to, or even above, the normal levels by addition of glucose to the incubation medium in vitro; under these circumstances, insulin had little further effect. Incorporation of phenylalanine -3-C^{14} into liver

and diaphragm protein fraction was depressed in severe diabetes to approximately the same degree as for glycine -1-C^{14}.

Amino acid uptake in vitro by liver and diaphragm of normal rats was reduced by previous fasting. This depot, in contrast to that in diabetic tissues, was corrected merely by the addition of glucose to the incubation medium, no insulin addition being required.

The depression of glycine -1-C^{14} uptake into glutathione, which was associated with diabetes, remained relatively the same when the glycine concentration in the incubation medium was increased by a factor of 40. The author concludes that the decrease in incorporation of glycine -1-C^{14} in diabetes is attributable in large part to decreased peptide synthesis. A limited concurrent increase in protein breakdown in the diabetic is not excluded.

Kuntze, J. (*Med. Klink des Allgemeinen Krankenhauses Langenhorn, Hamburg, Germany*): INSULIN LIPODYSTROPHY AND DIABETIC COMA. Therapie der Gegenwart *4*:149-50, April 1953.

The development of local tissue changes of the lipodystrophy type in diabetics injecting insulin is frequent, particularly in women and children. Their causes are unknown. Treatment with the known methods does not always lead to success. The patients must be admonished not to inject insulin into the lipomas because delay in absorption may occur which could bring about fluctuations and disruption of the metabolism.

Lazarus, Sidney S.; and Volk, Bruno W. (*Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N.Y.*): STUDIES ON HYPOGLYCEMIC RESPONSIVENESS. Metabolism *2*:500-09, November 1953.

Insulin tolerance tests using 0.1 unit per kg. of body weight were made on intact dogs, adrenalectomized controls and adrenalectomized dogs receiving Armour growth hormone daily (all adrenalectomized animals were given Percorten subcutaneously and also saline ad libitum), hypophysectomized dogs tested with and without daily ACTH, adrenomedullated, total sympathectomized, and both demedullated and sympathectomized dogs, normal dogs receiving tetraethyl ammonium chloride, hexamethonium, and benzodioxane, and finally depancreatized dogs receiving lecithin and insulin.

An attempt was made to differentiate by these studies, the mechanisms involved in the recovery phase of the blood sugar level during the insulin tolerance test. This phenomenon is termed "hypoglycemic responsiveness." All animals had this hypoglycemic responsiveness except the adrenalectomized dogs without growth hormone and the untreated hypophysectomized dogs. The authors infer that the mechanism for this must arise from a direct response of the liver by glycogenolysis to hypoglycemia. The endocrine balance maintains adequate liver glycogen on which the response occurs and the threshold blood sugar level at which it will occur.

Levin, Eugene B.; and Golum, Abraham (*Path. Ser. and Med. Serv., V. A. Hosp., Long Beach, Calif.*): THE HEART IN HEMOCHROMATOSIS. Am. Heart J. *45*:277-88, February 1953.

A case of hemochromatosis in a 36-year-old man is presented; it was characterized by diabetes, bronzing of the skin, cirrhosis of the liver with increased deposition of iron, and congestive heart failure. The course was rapid, and the patient died within 6 months from the onset of his original symptoms. At necropsy, the heart showed large amounts of iron in the myofibrils and interstitial cells and fatty degeneration of the myocardium. Focal necrosis of the anterior pituitary and absence of body storage fat were noted.

Link, R. P. (*Dept. of Veterinary Physiology and Pharmacology, Coll. of Veterinary Med., Univ. of Illinois, Urbana, Ill.*): A STUDY OF THE EFFECT OF REPEATED INTRAPERITONEAL INJECTIONS OF GLUCOSE IN PIGS. Am. J. Vet. Res. *14*:150-59, April 1953.

Twenty apparently healthy pigs were given daily intraperitioneal injections of glucose. The injection periods ranged from twelve to thirty-four days. Hyperglycemia persisted in 6 pigs after glucose injections were discontinued. Four other pigs became weak and comatose and died or were destroyed. The remaining 10 pigs developed mild hyperglycemia during the course of the injections, but the hyperglycemia did not persist after the injections were discontinued. Four pigs which showed persistent hyperglycemia in the postinjection period were subjected to intravenous glucose tolerance tests. The results of these tests indicated some impairment of carbohydrate tolerance. Glycosuria, ketonemia, and ketonuria were relatively mild in most of the pigs. Because of the apparent irregularity in the distribution of islets of Langerhans in the pancreas of the

pig, it was found difficult to make accurate appraisal of the extent of injury to these structures. In some islets, there appeared to be definite variation from the normal. There was some evidence of degranulation and degeneration of the cells. Lack of evidence of more hydropic degeneration may be due partly to the relatively short duration of hyperglycemia or the anatomical appearance of the cells may not be indicative of their functional capacity.

Marcovich, A. W.; and Marcovich, M. A. (*Dayton, Ohio*): DIKETOGULONIC ACID AND DIABETES MELLITUS. J. Lab. & Clin. Med. *42*:681, November 1953.

Diabetes mellitus has been produced in animals by injecting dehydroascorbic acid. One of the substances formed from dehydroascorbic acid is 2, 3-diketo-1-gulonic acid. By use of an original modification of existing procedures, diketogulonic acid was estimated in the blood of normal subjects and diabetic patients. None was found in 27 nondiabetics examined, but substantial quantities of diketogulonic acid or a closely related chromogen were found in all of the diabetics. The quantity determined seemed to have no relationship to the level of blood glucose or to whether or not the patient was receiving insulin.

Marsh, Julian B.; and Miller, Karen L. (*Dept. of Physiological Chem., Grad. Sch. of Med., Univ. of Pennsylvania, Philadelphia, Penn.*): DEMONSTRATION OF GLYCOGEN SYNTHESIS BY RAT KIDNEY SLICES IN VITRO. Science *118*:416-17, October 9, 1953.

The authors report optimal glycogen synthesis in rat kidney slices in vitro in a medium with an ionic composition in mM/1 of K+, 110; Mg++, 20 (or Ca++, 10); HCO_3, 40; Cl, 110; and *p*H 7.35, which conditions are virtually identical with those found optimal by Buchanan, Hastings and Nesbett for glycogen synthesis in rat liver slices as distinguished from the requirements for muscle glycogen synthesis.

Mayer, Jean (*Dept. of Nutrition, Harvard Sch. of Public Health, and the Dept. of Physiol., Harvard Med. School, Boston, Mass.*): GENETIC, TRAUMATIC AND ENVIRONMENTAL FACTORS IN THE ETIOLOGY OF OBESITY. Physiol. Rev. *33*:472-508, October 1953.

The author exhaustively reviews the subject of obesity, discussing its definition, the normal regulation of food intake, and the multiple factors classified as (a) constitutional, (b) traumatic, and (c) environmental which result in sustained hyperphagia and the breakdown in the normal regulation of energy metabolism, which brings about obesity.

McCandless, Esther L. (*Dept. of Physiol., Woman's Med. Coll. of Pennsylvania*): FACTORS INFLUENCING DEVELOPMENT OF INSULIN-INDUCED HYPOGLYCEMIC CONVULSIONS IN THE RABBIT. Proc. Soc. Exper. Biol. & Med. *84*:143-46, October 1953.

Of a group of 12 rabbits treated with "convulsive" doses of insulin, only 7 responded with convulsions. Except for the occurrence of convulsions, the reactors could not be distinguished from the nonreactors in the glycemic response to the first insulin injection, in response to epinephrine administration, or in liver glycogen. Significant differences were obtained in body weights and in the glycemic response to the second insulin injection. The latter was related to an unexplained increase in insulin sensitivity in the reactors. No change in sensitivity occurred in the nonreactors.

Metropolitan Life Insurance Co. (*New York, N.Y.*): THE CURRENT DIABETES PROBLEM. Statist. Bull. Metrop. Life Insur. Co. *34*:5-7, September 1953.

Diabetes remains a disease of major medical and public health interest. Of the chronic diseases common in middle and later life, it is not only one of the easiest to diagnose, but it also offers the best prospects of control in the individual patient. The list of causes of death among diabetics is becoming more and more like that among nondiabetics. A major portion of deaths in this broad category was accounted for by heart disease of the coronary type, a condition which occurs earlier and develops faster in diabetics than in nondiabetics.

The second largest cause in this category, accounting for nearly one-eighth of the deaths from all causes, was renal disease. Most of these fatalities were due to a serious complication, diabetic nephropathy, which is not perhaps the most important numerically among the causes of death peculiar to diabetes. A high proportion of deaths from this cause occurs among patients with long duration of the disease which began in childhood

or young adult life. To that extent it is a relatively new medical problem in diabetes and, because of its severity, is a source of major concern. Of approximately the same frequency as renal conditions were deaths of cerebral origin. In contrast, gangrene, formerly a frequent and dreaded complication of diabetes, caused only 1.3 per cent of all deaths in recent years.

Death from infection has been reduced to minor importance in the total mortality among diabetics, reflecting the generally improved condition of persons with the disease. Pneumonia and other nontuberculous respiratory diseases accounted for 4 per cent of the deaths and tuberculosis for only 1 per cent. Notable also are the low proportions of deaths from diabetic coma and insulin reactions. Diabetic coma, which, before insulin, was the major cause of death among diabetics, was responsible for only 1 per cent of the recent deaths. Even among patients with onset in childhood, only 6.7 per cent of the deaths were due to this cause. Fatal insulin reactions were few, accounting for only 3 out of the 1,358 deaths.

Mills, Morriss, Jr.; and Moore, Floy J. (*Dept. of Neuropsychiatry, V. A. Hosp., Houston, Tex.*): INVERT SUGAR IN INSULIN COMA THERAPY. Dis. Nerv. System *16*: 291-96, October 1953.

Four patients receiving deep insulin coma therapy received 100 cc. of 50 per cent glucose intravenously daily to terminate coma during a one-month study. Four other patients in the same insulin unit received 100 cc. of 20 per cent invert sugar for the same purpose. During the study it was found that there was no significant difference in the time required for clinical arousal from coma when invert sugar was used instead of glucose, and this was also true when the electroencephalogram was used to determine arousal. It was found that invert sugar was much less irritating to the tissues at the site of injection. Fifteen per cent fructose intravenously, regardless of the dose, requires about 20 to 30 minutes for termination of coma. This is roughly comparable to the time required for glucose by gavage to arouse the patient. Invert sugar gives a much more stable blood level immediately following injection than does glucose, and it is believed that this fact may, by elimination of compensatory hypoglycemia, help to prevent secondary comas. In view of the foregoing, it can be concluded that 20 per cent invert sugar is at least as effective as 50 per cent glucose in returning to consciousness patients in insulin hypoglycemia.

Mirand, E. A.; and Osborn, C. M. (*Syracuse Univ., Syracuse, N.Y. and the Roswell Park Mem. Inst., Buffalo, N.Y.*): INSULIN SENSITIVITY IN THE HEREDITARY HYPOPITUITARY DWARF MOUSE. Proc. Soc. Exper. Biol. & Med. *82*:746-48, April 1953.

Under the experimental conditions employed in these studies, findings may be summarized as follows: a) The insulin-hypersensitive hereditary hypopituitary dwarf mouse can tolerate only 3 per cent of the dose of insulin that produces comparable symptoms in normal mice (2 units of insulin per kg. of mouse weight). Higher dosages cause severe hypoglycemia followed by death. b) ACTH, adrenocortical extract (ACE), and cortisone act as anti-insulin agents as shown by their ability to increase blood-glucose levels and to reduce hypoglycemic convulsions. Desoxycorticosterone acetate and testosterone propionate exhibit no anti-insulin action. c) Factors that may be responsible for the hypersensitivity to insulin are discussed.

Mirsky, I. Arthur; Futterman, Perry; and Broh-Kahn, R. H. (*Cincinnati, Ohio*): THE QUANTITIVE MEASUREMENT OF VIBRATORY PERCEPTION IN SUBJECTS WITH AND WITHOUT DIABETES MELLITUS. J. Lab. & Clin. Med. *41*:221-35, February 1953.

The threshold of vibratory perception was measured quantitatively in 102 patients with diabetes and in 136 normal subjects by means of an inaudible electromagnetic vibrator. The threshold for the perception of vibratory stimuli increases with age. This increase is similar on both sides of the body, is greater in the toes than in the fingers, and is essentially the same in men and women. The presence of diabetes results in a marked impairment of vibratory acuity; but the influence of age remains unchanged, so that the patient with diabetes reacts as if he were approximately twenty years older in this respect than a person without diabetes. The impairment of vibratory acuity in patients with diabetes is not dependent upon either the duration or the severity of the metabolic syndrome and consequently should be regarded as a concomitance rather than a "complication" of the metabolic derangement due to insulin insufficiency.

Moncrief, J. A.; Coldwater, K. B.; and Elman, R. (*Dept. of Surg., Washington Univ. Sch. of Med., Barnes Hosp., St. Louis, and V. A. Hosp., Jefferson Barracks, Mo.*):

POSTOPERATIVE LOSS OF SUGAR IN URINE FOLLOWING INTRAVENOUS INFUSION OF FRUCTOSE (LEVULOSE). A. M. A. Arch. Surg. 67:57-60, July 1953.

Infusions on alternate days of 2 liters of 10 per cent fructose during 4 postoperative days in 10 patients revealed an average loss of sugar nearly 3 times greater with dextrose than with fructose. The difference on the first postoperative day was insignificant but on the fourth day was nearly five times greater with dextrose than with fructose. In 8 patients given 2 liters of 10 per cent fructose per day during 28 postoperative days, the mean daily loss of sugar in the urine was 7.9 gm.; in 21 patients given 3 liters containing fructose (250 gm.) and protein hydrolysate (Amigen, 50 gm.) during 34 postoperative days, the mean daily loss of sugar was 8.9 gm. This is one third the loss noted with a control group in which following the infusion of 2 liters of 10 per cent dextrose (200 gm.) given at a similar or slower rate the comparable figure was 26.2 gm. It is concluded that 10 per cent fructose given at a rate of two to three hours per liter in adult patients during the postoperative period is followed by a much smaller loss of urinary sugar than when 10 per cent dextrose solution is infused.

Monier, M. M.; and Weiss, R. J. (*Dept. of Biochemistry, Sch. of Med., George Washington Univ., Washington, D. C.*): INCREASED EXCRETION OF DEHYDROASCORBIC AND DIKETOGULONIC ACIDS IN URINE OF RATS AFTER STANDARDIZED TEMPERATURE SHOCK. Proc. Soc. Exper. Biol. & Med. 84:93-94, October 1953.

Adult albino rats were subjected to temperature shock by immersion in water at 60°C. for 15 seconds. Urinary excretion of dehydroascorbic and diketogulonic acids increased greatly over control values established before temperature shock.

Novelli, David G. (*Biochemical Res. Lab., Massachusetts Gen. Hosp., and the Dept. of Biological Chem., Harvard Med. Sch., Boston, Mass.*): METABOLIC FUNCTIONS OF PANTOTHENIC ACID. Physiol. Rev. 33:525-43, October 1953.

Nutritional deficiency of pantothenic acid may lead to a large variety of pathological changes in most tissues of the body, affecting particularly the adrenal cortex, the nervous system, the skin and hair, and antibody production. Most, if not all, pantothenate in tissues is bound as coenzyme A. The biosynthesis of coenzyme A is described. The fact is pointed out that any biochemical lesion in the enzymatic machinery for the biosynthesis of the coenzyme will produce symptoms of pantothenate deficiency without being alleviated by the administration of the vitamin.

A review of the general metabolic functions of coenzyme A is given and its significant role cited in acetylation reactions involving amino acids, acetylcholine, and detoxication, in the synthesis of cholesterol and adrenal steroids, in fatty acid oxidations, and in initiating activity in the Krebs cycle, the energy generating system of the body.

In view of the many fundamental biochemical reactions which are mediated by coenzyme A, the metabolically functional form of pantothenic acid, explanation is afforded for the multiplicity of pathological symptoms in the vitamin-deficient state.

Paley, Ronald G. (*Dept. of Med., Univ. of Leeds, England*): LIPODYSTROPHY FOLLOWING INSULIN INJECTIONS. Metabolism 2:201-10, May 1953.

Lipoatrophy due to insulin is a harmless complication, because no important structures are damaged. In this study no patient has shown muscle atrophy clinically. There is evidence that intramuscular injections of insulin may produce local necrosis. Simple lipoatrophy is annoying solely because of its disfigurement. This alone is likely to cause emotional upset in female patients, especially the young ones. Little factual support is presented for most of the theories concerning the cause of lipoatrophy. For example, it has been suggested that androgen formation may protect the adult male and lack of it may account for the frequency of lipoatrophy in children and women. Observations in only one patient in our series, an adolescent making a dramatic improvement during a late but active onset of secondary sex characteristics, could support such a theory. In none of the other males with lipoatrophy was the contention that this complication is a result of lack of androgen secretion supported. A diabetic patient suffering from local dermal reactions to insulin is extremely likely to exhibit some degree of lipoatrophy in the future. Since the atrophic type of lipodystrophy cannot be produced experimentally in animals, it appears reasonable that this baffling problem should be investigated in the human. The present study has shown that impurities in the insulin may still be a factor in causing

lipoatrophy. By the use of highly purified insulin in new diabetic patients, it should be possible to demonstrate the absence of this complication. If that is the case, the impurity in insulin may possibly be the lipolytic agent. Spontaneous improvement occurred in almost 30 per cent of patients suffering from this complication irrespective of type of treatment.

Paley, Ronald G.; Seligson, David; and Lukens, F. D. W. (*George S. Cox Med. Res. Inst., Univ. of Pennsylvania, Philadelphia, Pa.*): STUDIES ON AN UNIDENTIFIED PRODUCT OF ALLOXAN METABOLISM IN URINE. J. Biol. Chem. 200:443-50, January 1953.

Using a semiquantitative procedure of studying alloxan and alloxanic acid by alkaline hydrolysis to form oxomalonic (mesoxalic) acid, which in turn was separated by chromatography and measured colorimetrically, the authors found that normal urine contains no oxomalonic acid before hydrolysis. After hydrolysis, significant amounts of oxomalonate could be obtained from the urine of normal man and animals. The method did not demonstrate any significant difference in the yield of oxomalonate between normal and diabetic subjects. Following the administration of alloxan or sodium alloxanate to animals, the yield of urinary oxomalonate was increased twenty to thirtyfold. Uric acid was not a source of urinary oxomalonate under the conditions of these experiments. The nature of the precursor (or precursors) of urinary oxomalonate, obtained by alkaline hydrolysis, in humans and in normal or alloxan-treated animals is unknown.

Patterson, John W. (*Dept. of Anat., Sch. of Med., Western Reserve Univ., Cleveland, O.*): PREVENTION OF DEHYDROASCORBIC ACID DIABETES BY ATROPINE. Proc. Soc. Exper. Biol. & Med. 83:850-57, August-September 1953.

The administration of atropine before the intravenous injection of dehydroascorbic acid prevents diabetes. This effect of atropine is not observed in splenectomized rats.

Pfizer Spectrum (*Brooklyn, N. Y.*): THE SOMNOLENT METABOLIC RATE. J.A.M.A. 153:23, September 26, 1953.

While the diagnosis of clear-cut hyperthyroidism is seldom difficult, that of mild thyrotoxicosis is still a vexatious problem in clinical medicine. Often the physician is hard put to distinguish the true hyperthyroid from the emotionally unstable euthyroid patient. Other conditions associated with hypermetabolism, such as apprehension, fever, congestive heart failure, pregnancy, polycythemia, severe anemia, leukemia, diabetes, and Parkinson's disease, may also confound the judgement. In young children the problem is especially difficult.

In 1949, Elmer C. Bartels, in Boston, and U. Pegni, in Italy, began studying basal metabolic rates obtained under thiopental anesthesia. They reported that this technic generally winnowed the chaff from the genuine thyrotoxic grain. While true hyperthyroid patients showed only a small drop in basal metabolic rate or none after thiopental-induced narcosis, patients whose elevated metabolic rate stemmed from various emotional disturbances showed a drop to normal.

Further investigations have been reported by Richard L. Rapport, George M. Curtis, and Sarah J. Simcox, at Ohio State University, who studied 52 hyperthyroid, hypothyroid, and euthyroid subjects, and by Glauco Cernuschi, in Italy, who studied 23 children. These authors again demonstrated a fall in basal metabolic rate under anesthesia that was of small magnitude only in the thyrotoxic subjects; and they conclude that the method achieves a true basal state. Rapport and his coworker further simplified the technic employing intravenous pentobarbital. They believe that pentobarbital can safely be given in the office.

A critical evaluation of metabolic rates recorded under narcosis may eventually require a new set of standards. Meanwhile, the technic does appear to give a more reliable estimation of thyroid activity than the waking basal metabolic rate. Faced with a difficult differential diagnosis, the physician may secure the wanted information simply and conclusively with the aid of narcosis.

Planchart, Alfredo; and Villalba, Rafael (*Instituto Nacional de Nutrición*): EVOLUTION OF GLYCEMIA AND REDUCED GLUTATHIONE OF THE BLOOD FOLLOWING GLUCOSE LOAD. Archivos Venezolanos de Nutrición 3:45-52, June 1952.

The curves for glucose and glutathione concentrations of the blood of 40 diabetics and 20 healthy subjects were studied. It is found that the high values for glucose correspond with the low values for glutathione even

after the administration of glucose. It is possible that the curve of glutathione values after the administration of glucose to the diabetics is similar to the one obtained in the healthy subjects. It is concluded that there are several reasons to think that the low values of sulfhydril substances found in the diabetics are of importance in the etiology of the disease.

Queries and Minor Notes (*Cuthbert, Ga.*): HEADACHE IN DIABETIC AFTER EATING FATS. J.A.M.A. *153*:894, October 31, 1953.

Headache after the ingestion of fat is certainly unusual. It should be tested under controlled conditions before any drastic changes in diet are made. If it is actually true that all fats produce headaches in this patient, one would be justified in giving a high-carbohydrate diet (between 200 and 300 gm. a day) together with liberal amounts of protein (up to 125 gm. a day).

Queries and Minor Notes (*El Paso, Texas*): BRITTLE DIABETES. J.A.M.A. *153*:892, October 31, 1953.

Brittle diabetes, a term coined by Woodyatt, is manifested by wide variations in glycosuria and glycemia without obvious causes, such as variations in the composition and absorption of the diet, exercise, insulin, and infections or alterations in the activity of the pituitary, thyroid, adrenal, or liver. With more accurate and critical study such cases are encountered less frequently. The term "brittle diabetes," like that of acute fulminating diabetes, will probably gradually drop out of the literature.

Tendencies toward "brittleness" may be expected particularly in the young, the thin, the active (emotionally or otherwise), the unco-operative, or the discouraged patient who has become careless and often thoughtlessly breaks regulations. Children and thin adults who have severe diabetes have a low storage capacity for glycogen. Variations, therefore, in total food, carbohydrates, exercise, and insulin lead to a more prompt change in the blood sugar because the glycogen reserve is low.

It is probable that a diet suited to the metabolic needs of the patient, and containing about 150 gm. of carbohydrate, or even 100 gm. in a very small person, will lead to less variations in the blood sugar than one with 200 gm. or more. Adjustments must be made for exercise. Insulin usually will be required at least twice a day, preferably NPH insulin before breakfast and the evening meal, with additions to it of crystalline insulin as needed, morning and night.

Robillard, Rosario (*Hôpital Saint-Luc, Montreal*): REFLEXIONS ON INSULIN DOSES DURING SEVERE DIABETIC ACIDOSES. L'Union médicale du Canada *82*:13-16, January 1953.

The physician should remember that a diabetic who vomits or feels abdominal pain or experiences respiratory difficulty is a severely stricken patient and that to put off analyses and particularly to delay treatment to the next day is to sign the death warrant of this patient.

Rodriguez-Arias, B. (*Madrid*): INSULIN THERAPY IN MULTIPLE SCLEROSIS. Revista Clinica Espanola, *48*:228-32, February 28, 1953 [Abstr. from J.A.M.A. *152*:1486, August 8, 1953].

Six patients with typical multiple sclerosis were given doses of insulin to produce "subshocks," with neurosympathetic symptoms that did not approach the precoma or coma stages. The treatment was well tolerated, without accidents or complications. The author reported that the appetite, nutrition, and general condition of the patients improved over a period of several months and that pain, paresthesia, spasticity, and ataxia were diminished.

Rutman, Julia Z. (*Philadelphia, Pa.*): METHOD FOR THE DETERMINATION OF ACETONE IN TWO-TENTHS MILLILITER OF BLOOD. J. Lab. & Clin. Med. *41*:648-52, April 1953.

The author combines the method of Rappaport and Baner, distilling 0.2 mg. of whole blood after addition of sodium bisulfite without preparation of a filtrate, with the method of Lester and Greenberg, using 2,4 - dinitrophenylhydrazone as the trapping agent. The factors involved in the extraction of acetone 2,4 - dinitrophenylhydrazone by carbon tetrachloride were investigated. With this rapid method, complete recovery of acetone alone or acetone added to blood is claimed.

Samuels, Saul S. (*New York, N.Y.*): PROGNOSTIC VALUE OF THE ELECTRONIC OSCILLOMETER IN PERI-

PHERAL ARTERIAL DISEASES. Angiology 4:496-501, December 1953.

Twenty cases of peripheral arterial disease (8 diabetics and 8 with gangrene) with zero readings at the ankle obtained with a Tycos recording sphygmomanometer were tested simultaneously with an electronic oscillometer. None on the latter instrument recorded zero, and 9 recorded 20 or 20 plus. All with readings higher than 8 showed consistently good therapeutic results, including 4 with gangrene. The author concludes that a reading of 10 or more at the ankle level is justification for continuing conservative treatment, with an excellent chance of ultimate recovery without major amputation.

Sbordone, G.: LIPOID EXTRACTS AND THE RETINA. Archivio di ottalmologia 56:305-17, July-August 1952. [Abstr. from Am. J. Ophth. 36:1318, September 1953.]

The author has treated various diseases of the retina (myopic fundus changes, tapeto-retinal degenerations, chorioretinitis of vascular origin, diabetic neuroretinitis, senile and traumatic macular degeneration) and detachment which has been successfully treated surgically with subcutaneous injections of retinal lipoid extracts ("cellulin retinale"). He claimed that all 34 patients reported subjective improvement and that the majority showed some demonstrable improvement which was maintained after cessation of therapy, although the fundus changes remained unaltered.

Schwarz, H. P.; Riggs, H. E.; Glick, C.; McGrath, J.; Childs, R.; Bew, E., Jr.; and Stone, F. (*Divs. of Biochemistry and Neuropathology, Philadelphia Gen'l. Hosp.*): INFRARED SPECTROSCOPY OF LIVER GLYCOGEN IN NORMAL AND IRRADIATED ADULT AND FETAL RATS. Proc. Soc. Exper. Biol. & Med. 85:96-101, January 1954.

Frozen and dried sections of adult and fetal rat liver were studied by infrared spectroscopy. The infrared absorption band found at 9.70 to 9.60 μ was assigned to glycogen. Maternal fasting of 24 hours' duration reduced liver glycogen of the adult to a much greater extent than in the fetal liver. The relative amount of glycogen after sugar feeding was much higher in fetal than in adult liver. Quantitative studies of liver glycogen after x-ray irradiation showed the existence of an "acute" and "delayed" effect, the former decreasing and the latter increasing liver glycogen.

Scriver, Walter de. M.; and Trenholme, Jean (*Royal Victoria Hosp., Quebec, Canada*): THE DIABETIC AND HIS DISEASE. Canad. M. A. J. 69:477-80, November 1953.

The diabetic is beset by more problems than those which concern his diet and insulin. In treating the diabetic, it is well to remember that he is also a human being.

Sherrill, J. W.; and Wick, A. N. (*La Jolla, Calif.*): EFFECT OF PROLONGED ADMINISTRATION OF RADIOACTIVE ZINC ON THE PANCREAS. J. Lab. & Clin. Med. 41:40-42, January 1953.

Radioactive zinc^{65} acetate was administered to rats for a six-month period. There was no evidence that diabetes was produced, as indicated by normal growth curves, absence of glycosuria, and absence of high blood sugars. The authors do not discuss whether anatomical changes in the pancreas were produced.

Stadie, William C.; Haugaard, Niels; and Vaughan, Martha (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Pa.*): THE QUANTITATIVE RELATION BETWEEN INSULIN AND ITS BIOLOGICAL ACTIVITY. J. Biol. Chem. 200:745-51, February 1953.

By the use of isotopic insulin, the acceleration of glycogen synthesis by rat diaphragm per unit mass of bound insulin was measured. This value was found to be different in two strains of rats. There was no difference in binding of insulin under comparable conditions in the normal and hypophysectomized rat. However, the acceleration of glycogen synthesis per microgram of bound insulin was greatly increased following removal of the pituitary. The authors conclude that evidently pituitary hormone has contrainsulin action in the periphery.

Stewart, Ronald D.; and Roitman, Ellen. (*Dept. of Biochemistry, Dalhousie Univ., Halifax, Nova Scotia, Canada*): EFFECT OF PANCREATIC EXTRACTS ON KETONE BODY PRODUCTION OF RAT LIVER. Endocrinology 53:192-97, August 1953.

An investigation has been carried out with the hope of demonstrating a hypothetical ketone body regulating hormone of the pancreas which is not identical with insulin. By aqueous extraction of the gland, followed by other purification steps, an extract has been prepared which causes on the average a 30 per cent reduction in

the ketone body output of rat liver slices, provided that anterior pituitary extract is also present in the incubation medium. The extract also causes hyperglycemia in the fed, but not in the fasted, rabbit and exhibits no insulin activity in this species. Methods of preparation and testing of the extract are reported in detail.

Stutzman, F. L.; and Amatuzio, M. S. (*Minneapolis, Minn.*): BLOOD SERUM MAGNESIUM IN PORTAL CIRRHOSIS AND DIABETES MELLITUS. J. Lab. & Clin. Med. *41*:215-19, February 1953.

Blood serum magnesium was studied in 23 patients with portal cirrhosis and in 101 patients with diabetes mellitus. The values for 17 normal controls were 1.82 ± 0.12 mEq./L, for the patients with cirrhosis 1.49 ± 0.20, for the diabetics requiring no insulin 1.82 ± 0.18, requiring less than 20 units of insulin 1.72 ± 0.18, requiring between 20 and 40 units of insulin 1.66 ± 0.15, and for those diabetics requiring more than 40 units of insulin 1.67 ± 0.14 mEq./L. Increased values were found in the patients with diabetes plus renal dysfunction.

Styron, Charles W. (*Raleigh, N. C.*): THE PREVENTION AND TREATMENT OF DEGENERATIVE COMPLICATIONS OF DIABETES MELLITUS. South. M. J. *46*:1057-62, November 1953.

The author reports a study correlating the degree of control and the duration of diabetes with the occurrence of complications (retinitis, nephropathy, heart disease, neuropathy, and arteriosclerosis) in 519 cases under observation for 1 to 6 years, information about the remainder of their diabetic lifetime being secured by detailed questioning. The duration of diabetes ranged from 1 to 33 years with an average of 13.2 years.

The data demonstrate that complications increase both with progressive duration of the disease and with poorer regulation of the diabetes.

Turell, Robert (*New York, N. Y.*): CORTICOTROPIN AND CORTISONE IN INTRACTABLE ANOGENITAL PRURITUS. J.A.M.A. *152*:806-08, June 27, 1953.

Since the introduction of corticotropin (ACTH) and cortisone into clinical medicine and surgery, the author has observed several patients with refractory anal pruritus who have responded dramatically well to one or both of these hormones and others who have failed to be relieved appreciably. In the successful cases, the pruritus invariably recurred after variable periods of time following the discontinuation of therapy. In a case of diabetes, no exacerbation of the diabetes occurred.

Turnock, D. M.; and Welbourn, R. B. (*Liverpool, England*): THE EFFECTS OF GLUCOSE ON BLOOD PYRUVIC ACID LEVELS IN MILD THIAMINE DEFICIENCY. J. Lab. & Clin. Med. *42*:261-68, August 1953.

A test has been devised which provides evidence of early or mild thiamine deficiency. The blood pyruvic acid level is measured in fasting subjects after one hour's rest and again at one, two, and three hours after administration of 100 gm. of glucose by mouth. The subjects remain at rest throughout the test. Thiamine deficiency can be presumed if the blood pyruvic acid concentration fails to return to its basal level after three hours, even when the basal and peak levels are normal. In most cases, treatment with thiamine restores the curve to normal.

An analysis is given of 98 time curves showing the pyruvic acid content of the blood, after the administration of glucose in 32 subjects. The test has provided confirmation of a clinical diagnosis of thiamine deficiency (based on the response of specific therapy) in eight of ten cases and has given evidence of deficiency in cases where it had not been suspected.

Volk, Bruno W.; Lazarus, Sydney S.; and Goldner, Martin G. (*Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N. Y.*): ALPHA CELLS OF PANCREAS—MORPHOLOGIC AND PHYSIOLOGIC CONSIDERATIONS; A REVIEW. A. M. A. Arch. Int. Med. *93*:87-106, January 1954.

It can be concluded, from the authors' review, that contrary to general belief, the alpha cells of the pancreas apparently do not play a role in blood sugar homeostasis or in the production of the hyperglycemic-glycogenolytic factor of the pancreas (HGF). They are, however, a morphologic entity and, because of the presence of cytoplasmatic granules, are assumed to have a secretory function. At the present time, despite the abundance of experimental work, their physiologic status is unknown. A related problem, the site of origin of HGF, also remains to be elucidated. This problem seems particularly unique, since a hyperglycemic principle has been isolated from

pancreas in which the alpha or beta cells or the exocrine portion has been destroyed. It might be pointed out that other cellular systems of the pancreas, such as the D cells of the islets, the ductal tissue, or the paraductal insular organs (Feyrter) may serve as the source of the hyperglycemic principle. The outlook for clarification of these problems by further experimental work seems to be improved, since a simple chemical method for the destruction of the alpha cells is now available.

Waddell, William R.; Geyer, Robert P.; Clarke, Edith; and Stare, Fredrick J. (*Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.*): ROLE OF VARIOUS ORGANS IN THE REMOVAL OF EMULSIFIED FAT FROM THE BLOOD STREAM. Am. J. Physiol. *175*:299-302, November 1953.

The effects of evisceration, hepatectomy, splenectomy, nephrectomy, and enterectomy upon the disappearance of intravenously administered emulsified fat from the blood stream were studied. The liver and spleen remove a major portion of such fat, but other tissues are capable of removing small quantities. Removal of the splanchnic viscera and impairment of hepatic function affect the normal relationship between concentration and removal of fat so that the clearance of fat particles is no longer a first-order process.

Weaver, William A., Jr. (*Philadelphia, Penn.*) DIABETES IN CHILDHOOD. The Hahnemannian *88*:166-68, October-December 1953.

The successful treatment of diabetes in childhood combines a special understanding of the disease process in the child and an appreciation of his attitude toward the disease, toward treatment, toward his playmates, and toward life. The little patient's confidence must be gained. The regimen should be as flexible as is practical and should be arranged to permit a reasonably normal life.

The author considers the following essential for good control:

1. Adequate nourishment.
2. A fasting blood sugar level below 150 mg. per 100 cc. and postprandial levels below 200.
3. Freedom from consistent glycosuria.
4. Cholesterol content of the blood below 230 mg. per 100 cc.
5. Normal physiologic, psychologic adjustment and development.

In the very rare case of diabetes in infancy, 1 to 2 units of regular insulin per kg. of body weight may be needed in frequent small doses. U-10 insulin can be made by dilution of U-40 regular insulin with sterile water; it can be given with a tuberculin syringe if necessary. From 10 to 20 units may be needed per day, divided into 4 or 5 doses before feeding periods.

As the child grows, his requirement for food as well as for insulin gradually change, and the diet should be reviewed at intervals of not longer than every six months for changes in weight and age; as adolescence is passed, the diet should be based on adult requirements.

Weisler, Morris J. (*New Orleans, La.*): THE ROLE OF POTASSIUM IN DIABETIC ACIDOSIS. Louisiana M. Soc. *105*:417-21, November 1953.

Potassium should be administered orally or parenterally about four to six hours after therapy of diabetic acidosis has been instituted, if adequate diuresis has been obtained. The author cautions against the intravenous administration of potassium by those who are not familiar with the possible complications and who do not have adequate control facilities.

Weiss, Morris M.; and Gray, William R. (*Louisville, Ky.*): INCIDENCE OF HYPERTENSION AND DIABETES IN NEGROES WITH ACUTE MYOCARDIAL INFARCTION. J. Lab. & Clin. Med. *42*:966, December 1953. (Abstract from Proceedings of 26th Annual Meeting, Central Society for Clinical Research.)

A study was made of the frequency of antecedent hypertension and/or diabetes in acute myocardial infarction in Negro men and women. In 90 per cent of each sex, hypertension and/or diabetes preceded the attack. The incidence of these factors in Negro men is similar to their incidence in white women who have had an acute myocardial infarction.

Westermeyer, V. W.; and Raben, M. S. (*Dept. of Med., Tufts Coll. Med. Sch., Boston, and Ziskind Res. Labs., New England Center Hosp., Boston, Mass.*): FALL IN BLOOD SUGAR FROM ANTERIOR PITUITARY EXTRACT. Endocrinology *54*:173-80, February 1954.

Anterior pituitary preparation purified by the glacial acetic acid-oxycellulose method lowered the blood sugar concentration by 15 to 55 per cent in one hour in intact

unfasted mice, from 10 to 60 per cent in adrenalectomized mice receiving saline, and from 10 to 40 per cent in similarly treated mice receiving cortisone in addition and inhibited the effect of insulin in adrenalectomized mice.

White, Priscilla; Koshy, Phillip; and Duckers, Janine (*Joslin Clin., Boston, Mass.*): THE MANAGEMENT OF PREGNANCY COMPLICATING DIABETES AND OF CHILDREN OF DIABETIC MOTHERS. M. Clin. North America pp. 1481-96, September 1953.

The authors outline the four objectives in the management of the pregnant diabetic. Maternal survival over a 20-year period is analysed, and the statistics of survival are presented. The relation of retinopathies and nephropathies to pregnancy is discussed and statistics presented for cases seen before and after the advent of treatment with sex hormones. Fetal wastage is discussed in relation to the degree of vascular disease and the duration of gestation.

The management of pregnancy complicating diabetes is discussed under six headings: (1) The evaluation and classification of the patient. (2) The dietary and insulin treatment. (3) The treatment of edema and hydramnios. (4) The basis for sex endocrine therapy, with an outline of treatment. (5) The indications for pelvic delivery vs. cesarean section and the timing of delivery. (6) Three explanations for poor fetal behavior.

The subsequent course of 105 children of diabetic mothers is presented. They found superiority of growth in stature and weight, a tendency toward development of hyperglycemia and glycosuria, and a well-defined change of the vascular pattern of the smaller vessels of the conjunctiva. In this group, diabetes was found 225 times as commonly as in the general population.

Wick, Arne N.; Morita, Toshiko N.; and Joseph, Lionel (*Scripps Metabolic Clin., La Jolla, Calif., and San Diego State Coll., San Diego, Calif.*): THE OXIDATION OF MANNITOL. Proc. Soc. Exper. Biol. & Med. 85:188-90, January 1954.

Mannitol has been said to be of not much importance as an adjunct to the diabetic diet, since 80 per cent or more of the mannitol administered is excreted in the urine; but these conclusions apparently have been based on data obtained by intravenous administration. To study this point uniformly labeled C^{14} mannitol carbon was administered to rats. When given orally, about 50 per cent of the mannitol carbon was recovered in the expired CO_2 in 12 hours. By intraperitoneal injection, the mannitol was largely recovered in urine, with only 2 to 3 per cent of the mannitol carbon recovered in the expired CO_2. By injection directly into the portal system by way of the spleen, oxidation comparable to or greater than that obtained by oral administration was obtained. The authors concluded from these results that mannitol can be oxidized by the body if it is administered by a route that makes it first available to the liver, as in oral feedings.

Wool, Ira G.; and Goldstein, M. S. (*Dept. of Physiol., Univ. of Chicago, and the Dept. of Metabolic and Endocrine Res., Med. Res. Inst., Michael Reese Hosp., Chicago, Ill.*): ROLE OF NEUROHUMORS IN THE ACTION OF THE ADRENAL CORTICAL STEROIDS: MOBILIZATION OF FAT. Am. J. Physiol. 175:303-06, November 1953.

The development of a fatty liver which follows the administration of ethionine to fasted female rats was found to be inhibited by adrenalectomy. Neither cortisone nor epinephrine alone restored the ability of the adrenalectomized rat to develop a fatty liver following ethionine treatment. When cortisone and epinephrine were administered together, however, an amount of fat appeared in the liver comparable to that observed in the normal. It is postulated that the well-established inability of adrenalectomized animals to mobilize fat represents an altered sensitivity to the action of the neurohumor, epinephrine, which sensitivity is restored by presumably physiologic doses of cortisone, and which doses are ineffective by themselves.

Wyshak, G. H.; and Chaikoff, I. L. (*Dept. of Physiol. of the Univ. of California Sch. of Med., Berkeley, Calif.*): METABOLIC DEFECTS IN THE LIVER OF FASTED RATS AS SHOWN BY UTILIZATION OF C^{14} LABELED GLUCOSE AND FRUCTOSE. J. Biol. Chem. 200:851-57, February 1953.

The utilization of C^{14} labeled glucose and fructose was studied in liver slices prepared from normal nonfasted rats and from rats fasted 48 to 72 hours. The conversion of the added glucose to carbon dioxide, fatty acids, and glycogen was depressed in the liver of the fasted rat. The recoveries of C^{14} glycogen and $C^{14}O_2$ from radioactive fructose proceeded at normal ratio in livers from fasted rats, but lipogenesis was impaired. On the basis

of their findings, the authors postulate a block in the liver from the fasted rat at the glucokinase reaction. A second block in the synthesis of fatty acids at or beyond the C_2 fragment level (acetyl coenzyme A) was invoked to explain the inhibition in lipogenesis. The authors point out that the defects or blocks demonstrated here for the liver of the fasted rat in glucose utilization resemble those previously reported for the liver of the glucose-fed, alloxan-diabetic rat. Glucose administration alone completely restored to normal the utilization of added glucose by liver from the fasted rat.

Yager, Isadore (*New Orleans, La.*): RAPID DETERMINATION OF BLOOD ACETONE AND BLOOD GLUCOSE. J. Lab. & Clin. Med. *42*:474-78, September 1953.

A rapid qualitative test for blood sugar and acetone levels, based on a modification of Kleeberg-Moore's acetone test, is presented. The former test involves precipitation with trichloracetic acid and development of color due to glucose in the filtrate by boiling with alkali. The same filtrate is used for determining the presence of acetone by the standard "ring" test with nitroprusside and ammonia.

Zieve, Leslie; and Hill, Earl. (*Dept. of Med. and the Radioisotope Unit, V. A. Hosp., and the Univ. of Minnesota, Minneapolis, Minn.*): COMPARATIVE IMPORTANCE OF SEVERITY AND THERAPEUTIC EFFORT IN DETERMINING THE OUTCOME OF DIABETIC ACIDOSIS AS OBSERVED IN A REPRESENTATIVE GROUP OF PATIENTS. J. Lab. & Clin. Med. *43*:107-12, January 1954.

Seventy-seven case histories of diabetic acidosis were reviewed in order to estimate the relative importance of severity factors and of therapeutic effort in determining the outcome. Fifty-one patients who lived were compared with 26 who died. Large differences were found between the two groups with the important severity factors but not with the therapeutic measures. In this series the more severe cases received essentially the same treatment as the milder cases. The authors urge that the severity factors be evaluated in each case of diabetic acidosis in order that more vigorous early therapy would be used in the more severe cases.

Zöllner, Georg; and Schröder, **Henning** (*Pharmacol. Inst., Hamburg Univ., Hamburg, Germany*): INVESTIGATIONS OF THE INFLUENCE OF PERIDURAL ANESTHESIA UPON BLOOD SUGAR AND OF THE RESORPTION OF OLD INSULIN FROM THE PERIDURAL SPACE. Archives internationales de pharmacodynamie et de thérapie *92*:163-71, 1952.

Investigations were made as to the blood sugar level during peridural anesthesia in dogs as well as experiments as to the resorption of old insulin from the peridural space. These showed: 1. The blood sugar level does not change under peridural anesthesia. 2. The regulation capability of the organism for the blood sugar level is not impaired by intravenous glucose or insulin burdening. 3. Insulin introduced into the peridural space takes effect faster than insulin administered subcutaneously. The blood sugar course upon peridural insulin administration resembles that of intravenous administration of the hormone. 4. No definite conclusions could be drawn from the present experiments as to the extent of the exclusion of the vegetative nervous system through peridural anesthesia. The sympathetic nerve probably was not influenced to a sufficient extent.

Zucker, Howard D. (*Diabetes Clin., Mt. Sinai Hosp., New York, N. Y.*): CARDIAC AND VASCULAR ACCIDENTS IN INSULIN-TREATED DIABETICS. Trans. Am. College Cardiol. *2*:96-103, 1952.

In elderly people the high incidence of vascular disease predisposes to just those accidents which may be precipitated by hypoglycemia. Here, particularly, one should weigh protection from cardiac and vascular accidents against the desirability of freedom from glycosuria and hyperglycemia and near normal blood sugars. Certainly the choice of the type of insulin to be used for this group should be made with the dangers of hypoglycemia in mind. Should the old patient with a notoriously capricious appetite be imprisoned by the demands of a long-acting insulin, or can a shorter-acting insulin keep him out of trouble? An incidental reminder is that in these days of personnel shortage the hospital may offer little protection against the dangers of insulin hypoglycemia; delay in testing urine specimens or in reporting, and the irregularity of the arrival of food on the floors can seriously interfere with diabetic management.

EDITORIALS

TESTOSTERONE TREATMENT OF HEMOCHROMATOSIS

In recent years there have been reports[1] suggesting that in patients with hemochromatosis the use of testosterone may be of benefit, at least symptomatically, with apparent improvement in strength and sense of well-being. Such beneficial results have been thought to be related to the gonadal hypoplasia commonly seen in hemochromatosis and to the anabolic effect of testosterone on protein metabolism. Consequently, the paper of Pirart and Franken[2] of the Brugmann Hospital in Brussels is of interest.

They studied 9 patients with proven hemochromatosis of whom 7 were men aged 44 to 70 years and 2 were women aged 56 and 59 years, respectively. The iron content of the serum of the 9 patients averaged 225 gamma per cent (range = 40 to 360 gamma per cent) whereas that of 10 normal subjects averaged 84 gamma per cent. The oral administration of 176 mg. of bivalent iron as ferrous gluconate did not cause any elevation of serum iron during the 4 hours following ingestion. However, when 20 mg. of iron in the form of an organic compound only slightly ionizable, were given intravenously and the iron content of the serum determined at 5 and 120 minutes following injection, a characteristic curve was obtained in both normal subjects and in patients with hemochromatosis.

Patients were then treated by injection of testosterone propionate in dosage of 50 mg. twice weekly for 3 weeks. No effect was seen clinically. At the end of the treatment period, iron was again injected intravenously in order to obtain tolerance curves to compare with those secured prior to testosterone treatment. A moderate though definite average lowering of the curves was obtained suggesting that, if anything, iron found its way more readily into the tissues following a course of testosterone treatment.

As the result of these studies, the authors conclude that the giving of testosterone has no specific benefit in hemochromatosis and that it may even act deleteriously by favoring the transfer of iron from the blood into the tissues. However, since in the oral tolerance test, no change in serum iron was obtained and since there is no evidence that testosterone favors the absorption of iron from the intestinal tract, there would appear to be no basis for fearing aggravation of hemochromatosis by testosterone unless iron is being administered parenterally. The real value, if any, of testosterone in the treatment of hemochromatosis awaits further study.

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TRYPSIN TREATMENT OF SUPERFICIAL GANGRENOUS LESIONS

The vulnerability of the lower extremities of older diabetics, on account of the tendency of the skin and subcutaneous tissues to become necrotic following local injury or infection, represents one of the major problems relating to diabetes today. When there is no serious impairment of the circulation and when the lesion is not extensive, conservative measures may lead to separation of the necrotic tissue and subsequent healing. However, even with thorough control of the diabetes with diet and insulin and the effective use of antibiotics to combat infection, a prolonged period of hospitalization may be necessary. Every physician or surgeon responsible for

the care of diabetic patients with lesions of the feet will welcome any form of treatment which may improve results or shorten the prolonged period of disability.

Surgical debridement has been disappointing unless the lesion is such as to permit total excision and immediate split-thickness graft and this is the rare type of lesion. Chemical or enzymatic dissolution of the necrotic tissue has likewise given unsatisfactory results up to this time. Encouraging results following the use of trypsin are reported by Pote elsewhere in this issue. My limited experience with this agent has been less impressive. The true value of this method will be indicated by the role it plays in the management of these lesions in well-organized diabetes clinics in the years ahead.

Until the efficacy of this or any unproven method of local therapy is definitely established, great care must be exercised by all concerned lest injudicious or unnecessarily prolonged trial of enzymatic treatment may lead to unnecessary expense to the patient, delay in the institution of radical treatment when indicated and even to unnecessary loss of limb or life.

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INSULIN-ZINC SUSPENSIONS

Insulin-zinc suspensions may soon complicate the depot-insulin situation still further. Eighteen years after the development of the first depot preparation, just as clinicians began to feel secure in the possession of an array of different insulins which fit the needs of practically all diabetics under all conditions, new preparations now enter the scene. If they had been discovered twenty years ago, it seems doubtful that any of the protein depot insulins would have emerged at all.

In 1935 D. A. Scott and A. M. Fisher, working in Dr. Best's section of the Connaught Laboratories, showed that the addition of a relatively large amount of zinc (0.01 per cent) to solutions of insulin caused a great prolongation of the action of insulin when injected subcutaneously in rabbits[1].

About two years ago Hallas-Møller and his colleagues at the Novo Terapeutisk Laboratories in Copenhagen, reported the precipitation of insulin in simple combination with zinc in the form of amorphous ("semi-lente") and crystalline ("ultra-lente") suspensions[2]. The amount of zinc required for precipitation in insoluble form is in the range of 0.5 to 2 mg. per 1000 units. Amorphous precipitation then occurs at *p*H 4.5 to 8 and crystals form at *p*H 5 to 6. Suspensions of the amorphous material show time-action only slightly more prolonged than that of insulin in solution, but suspensions of the crystalline preparation act in a true depot-insulin manner, with timing similar to that of protamine zinc insulin. Mixtures of the two types of material in proportions of about 30 per cent amorphous and 70 per cent crystalline material give a suspension, called "insulin lente" by the Novo Laboratories, which has an intermediate type of action similar to that shown by NPH, globin and protamine insulin mixtures in common use.

Clinical confirmation of the timing features of these three new preparations was quick to appear[3]. It was claimed that some patients with severe diabetes showed better control, chiefly with the "lente" or intermediate form. Local allergic reactions were said to be less common than with insoluble protamine modifications. Experimentation with various extemporaneous mixtures of the amorphous and crystalline forms to suit individual diets and patients has begun, chiefly in Great Britain. Clinical trials in the United States are now under way. The report to appear in a coming issue of DIABETES by Peck et al summarizes current data and adds significant new evidence on timing[4].

A judicial appraisal of the potential practical benefits of these new preparations must await further clinical trials. It seems clear at the present time, however, that any required timing can be produced with only the aid of zinc and control of the *p*H, and that the protein-precipitated insulins could be replaced with such suspensions, if this were desired. It remains to be determined whether predictability of action can be improved or consistency of response enhanced.

Several words of caution should be expressed to those clinicians who may use these new preparations in comparison with standard insulins. The addition of regular insulin to any of them may yield surprising results. They are suspended in an acetate buffer; this permits the insulin-zinc crystals to remain constant in size and form. Alterations in zinc content may change them and therefore the rate at which they go into solution or release their insulin after injection. Acid solutions of ordinary insulin added to insulin-zinc suspensions may alter the zinc content of the crystals, and therefore their physical form and rate of action. In other words, if the Novo preparations (or any similar products) are used they must not be altered much in *p*H nor mixed with phosphate buffer, or their time-action will be changed radically. Finally, if the views of this commentator are fairly representative of those of clinicians in the American Diabetes Association, the insulin manufacturers are begged to be cautious, in their zeal to be

first with the newest, about adding other insulins to the present ample market. Hopeless confusion can outweigh minor advantages of new products. Five standard insulins are now available in this country. Most of them are now familiar to practicing physicians and their patients. Those insulins and their combinations can do anything for any diabetic patient that is planned by informed physicians. Few disadvantages are inherent in them. In the various fields in which they are indicated they are fairly consistent, reliable and predictable in action and performance.

Before new preparations are introduced, it should be clearly apparent that they possess decisive advantages over those now available. If that is determined to be a fact, it would be desirable to introduce the new insulins to *substitute for and replace* existing preparations. More need not be added. If those which they replace could be withdrawn from the market, with the simple assurance that the new preparations will do the same job better, and can be substituted directly in the management of individual diabetic patients, the new preparations could simplify rather than confuse the commercial insulin situation.

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THE WORLD MEDICAL JOURNAL

The first number of the World Medical Journal appeared in January 1954. This new Journal has replaced the Bulletin of the World Medical Association as the official publication of that organization. Austin Smith, M.D., Editor of the Journal of the American Medical Association, is the Executive Editor; Louis H. Bauer, M.D., a past President of the American Medical Association and currently Secretary-General of the World Medical Association, is the Business Manager. The Editorial Board consists of Hugh Clegg, M.D., Editor of the British Medical Journal, Paul Cibre, M.D., of France, and Lorenzo Garcia-Tornel, M.D., of Spain. It is expected that the Council of the Association will eventually choose a group of collaborating editors who will give wider representation of the medical world. The text of the Journal appears in three languages—English, French and Spanish. It will be published bimonthly, but it is hoped that it will eventually appear each month. The first number contained original articles concerned with relations between the medical and nonmedical press, medical aspects of social security and the utilization of psychiatry in the daily practice of medicine. It presented a calendar of medical and scientific meetings.

The World Medical Association is a unique organization since its members are national medical societies. It represents no governmental agency. In this respect it is unlike the World Health Organization which represents governments. It has conducted surveys and taken part in discussions and decisions on such issues as standards of medical education, the effect of social security on medical practice, the status and distribution of hospitals and medical manpower. It adopted a Universal International Code of Medical Ethics. In some countries, including the United States, there are special committees of physicians who participate in the support of the World Association because of their interest in the interchange of medical ideas.

Membership dues in the United States Committee are $10.00, of which $5.00 is paid as subscription to the World Medical Journal. Correspondence relative to membership in the United States Committee should be addressed to the World Medical Association, 345 East 45th Street, New York 17, N. Y.

Rollin Turner Woodyatt

Arthur R Colwell, M.D., Chicago

Rollin Turner Woodyatt died in Chicago on December 17, 1953, at the age of 75. His long career was notable for achievements in the care of diabetic patients, in research both experimental and clinical, in the teaching of medical students and physicians and for a share in the early development of the American Diabetes Association.

Woodyatt was born June 3, 1878, in Chicago. Except for periods of study abroad, he made his home in Evanston and Chicago during his entire lifetime. His father, William Henry Woodyatt, was a physician who died in middle age. His mother lived a long time, was his confidante and companion, and he was devoted to her. She was the sister of the famed Chicago planner and architect, Daniel H. Burnham, who had a deep influence in Rollin Woodyatt's early life and later philosophies. In fact, it was concern for his uncle's welfare which influenced him to spend his life in the study and treatment of diabetes. There were no sisters, and only one brother, Ernest, an architect, who lived to middle age, like his father. Rollin Woodyatt virtually adopted his family.

In his early adulthood the discovery of an albuminuria, then thought to represent a hopeless chronic disease, led him to believe that he had only a short time to live. Those who knew his idealism, ambition and determination will readily understand how his entire life became affected by this outlook. He felt that he must accomplish much in a short time, sacrifice a family of his own, and consider time and effort no object whatsoever. The fact that the condition proved to be transient and harmless then permitted a full lifetime of accomplishment, for the pattern was set.

After his college work at Cornell and his medical training at Rush Medical College, he studied in the field of carbohydrate metabolism under the great organic chemist Nehf at the University of Chicago. This was followed by a period of study in Vienna. His greatest research training, however, was in Munich, working under the famous physician and investigator in metabolism, Friedrich Mueller. He enjoyed relating how he worked as a technician doing countless uric acid determinations, ignored in a corner of the laboratory, until after six months Mueller let him know that he had successfully withstood the tests of thoroughness and patience. He then accepted him in his own research in an intimate preceptorial relationship.

On his return to this country, Rollin Woodyatt worked at Presbyterian Hospital under Frank Billings and James B. Herrick, but his interest in research and diffidence towards practice soon made him independent. Research support became available and many productive years followed, involving laboratory studies, for the most part, of the chemistry and physiology of carbohydrate metabolism and experimental forms of diabetes. This period of investigation was followed by a tour of duty in the First World War, in which he became a Major in the United States Army.

Soon after his return to Chicago, the discovery of insulin in 1921 precipitated radical changes in his career. His laboratory and hospital beds at Presbyterian were the source of reliable and priceless early studies of the use of this hormone. The Chicago area was dependent upon him, in fact, for life-saving supplies of it before it became available in the market. Thereafter his private practice grew steadily and his time for research diminished. Some patients still were forgotten because of his intensive study of others, with no consciousness of passage of time on his part. Indeed, it was characteristic of him to be oblivious of all elements of time and schedule, primarily because of the intensity of his preoccupation with problems at hand and lack of concern for practical considerations. There are many amusing stories of his apparent forgetfulness. But he did not forget; he had

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simply not even become aware in the first place, because of prior interest in something else. Not many understood this. Some were antagonized by it unless they, themselves, became the object of his preoccupation and concentrated study. Then they became admirers.

During this clinical period of his career, there were literally hundreds of pupils at Rush and Presbyterian who came into close contact with him professionally and tutorially. He studied most of them thoughtfully, inspired them critically, and trained them meticulously by personal effort—again without regard for time, energy or expense. His was a one-pupil school with one brilliant and uncompromising preceptor. His exhaustive methods of logical and analytical study are responsible for a multitude of careful observations, correct deductions and new discoveries by the beneficiaries of his training.

His inventive genius was demonstrated repeatedly in the devising of new apparatus and development of new methods for the treatment of disease. He wrote beautifully and painstakingly, on scientific and nonscientific subjects alike. I have seen him spend one entire afternoon and evening without food, writing and revising a single paragraph, and days writing a paper only to tear it up and start over again. In this, as in everything else, he adhered stoutly to a conviction that nothing he did was perfect, that everything could be improved (given time and the will to do it) and that practically everything was worth that effort or it should not have been undertaken in the first place. In this he was utterly merciless in his criticism of himself and genuinely bewildered if it was resented when directed at the efforts of others. In his mind it was the product that mattered, not the feelings of the one who produced it.

During his professional career he was offered several chairs of medicine, declining them all except for one brief sojourn of duty as head of the department in his own school—Rush Medical College. He preferred learning and teaching over practice, and each of them over administration, the practical aspects of which confused him and were likely to be neglected. He served in several other distinguished offices including the presidencies of the Institute of Medicine in Chicago in 1941, the American Society for Clinical Investigation in 1916 and the Association of American Physicians in 1936. On two occasions he acted as physician in chief *pro tempore* at the Peter Bent Brigham Hospital in Boston where he had many intimate friends. He held the post of Director of the Sprague Memorial Institute Laboratory for Medical Research.

Woodyatt was a member of the Council of the American Diabetes Association at the time of the founding of the organization. He served in this capacity for six years. He was the Banting Memorial Lecturer at the annual meeting of the Association in Chicago in 1948.

His knowledge of art and architecture was impressive, his taste in literature exquisite and his enjoyment of competition in sports and games keen. He was a good mathematician, an able psychologist, a stern disciplinarian, an efficient organizer and shrewd judge of people and their faults and virtues. Friendship had to be won from him by unselfish motives and intellectual honesty. But his friends, thus accepted, then always were the object of generous support and fierce loyalty. Those who failed to keep faith were simply ignored without pretense. Some were offended by critical attitudes which were completely impersonal, but his friends learned to accept these as purely academic and objective, often learning something valuable therefrom. He was the soul of integrity—an aristocrat in behavior and human relations. His career is the perfect example of a medical life carefully balanced to include generous amounts of each of its three vital ingredients, namely, research, teaching, and care of patients. In other words, he accepted the obligation to discover new things, to teach what he learned, and to apply what he knew in practice.

According to my standards, his was the finest medical mind Chicago has produced in this century, and many of his colleagues and students have been profoundly influenced by it. Too often are the great works of a scholar such as this paid little heed until a time like the present. Then all too little can be said in tribute, and all of it must be said after he has gone. Rollin Woodyatt was completely satisfied with the results which he knew and saw. He craved no applause and was embarrassed by expressed gratitude. He was amply rewarded, I know, by the certainty that he exerted constructive forces at fundamental levels. The results and potentials of these gave him great satisfaction.

The life of such a talented person will not go unrecognized, of course. Rollin Woodyatt's monuments are scattered all over the country and the world, chiefly as physicians who have their feet on the ground, their hearts clean, and their eyes looking forward. In his own circle, each of them exerts influences for good which have been learned from the preceptor who took such pains with them. Thus his fine ideals are spread endlessly. So are the fruits of his investigation. *These* are his children. They, and their products in turn, always will be immortal reminders of a completely dedicated man—a scholar, artist, scientist, gentleman and thoroughbred.

Organization Section

Program of the 14th Annual Meeting of the American Diabetes Association June 19-20, Fairmont Hotel, San Francisco, Calif.

The American Diabetes Association will be honored to have Sir Henry Hallett Dale, O.M., G.B.E., M.D., F.R.S., F.R.C.P., eminent British physiologist, deliver the Banting Memorial Lecture at its Fourteenth Annual Meeting. His lecture, "Hormones of the Pituitary Posterior Lobe," will be given at the Joint Scientific Session of the Association and The Endocrine Society on Saturday afternoon, June 19. That evening, at the annual banquet of the Association, he will speak informally on some early memories of the discovery and development of insulin which he saw in Toronto in September, 1922, and with which he was concerned in England during the following year. In the past, Sir Henry has been the recipient of many honors in the field of medicine and physiology, including a share of the Nobel Prize for Medicine in 1936. Formerly Director of the National Institute for Medical Research, he is now Chairman of Trustees, The Wellcome Trust, London, England.

In addition to the Scientific Sessions, details of which follow, the schedule of events of the Fourteenth Annual Meeting includes the following occasions, to be held in the Terrace Room of the Fairmont Hotel unless otherwise indicated:

Registration: June 19-20, 8:30 a.m.—5:30 p.m., Lobby

Social Hour: Saturday, June 19, 6:30 p.m.

Banquet: Saturday, June 19, 7:15 p.m.

Annual Business Meeting: Sunday, June 20, 2:00 p.m.

At the banquet on Saturday, June 19, Randall G. Sprague, M.D., President of the American Diabetes Association, will speak. The Banting Memorial Medal will be presented to Sir Henry Hallett Dale, who will deliver remarks on "The Changing Outlook in Medicine."
There will be a special presentation to Mr. Herbert H. Marks, Manager, Insurance Medical Statistics, Metropolitan Life Insurance Company, New York City, for his outstanding contributions to the American Diabetes Association as Chairman of the Committee on Statistics.

SCIENTIFIC SESSION

Saturday, June 19, 2:00 P.M.

Joint Meeting with The Endocrine Society

RANDALL G. SPRAGUE and EARL T. ENGLE, Presiding

Some Effects of Growth Hormone on the Structure and Function of the Islets of Langerhans

LESLIE L. BENNETT (by invitation), JAMES H. R. SUTHERLAND (by invitation), and ADRIENNE A. BATTS (by invitation), University of California Medical School, Berkeley, Calif.

Discussion opened by JANE A. RUSSELL (by invitation), Emory University, Atlanta, Ga.

The Ketogenic Activity of Corticotrophin in the Rat

FRANK L. ENGEL and MILDRED G. ENGEL, M.S. (by invitation), Duke University School of Medicine, Durham, No. Car.

Discussion opened by E. B. ASTWOOD (by invitation), Tufts College Medical School and New England Center Hospital, Boston, Mass.

Metabolic Adjustments During Stress: The Effect of Intravenous Glucose on Pyruvate During Compound F Intusion

THOMAS F. FRAWLEY, JOHN JOSEPH GARRETT, Jr., (by invitation), and PAUL R. ROSCH (by invitation), Albany Medical College, Albany, N. Y.

Discussion opened by PETER H. FORSHAM, University of California Medical School, San Francisco, Calif.

BANTING MEMORIAL LECTURE

Hormones of the Pituitary Posterior Lobe

SIR HENRY DALE, O.M., G.B.E., M.D., F.R.S., F.R.C.P., Chairman of Trustees, The Wellcome Trust, Formerly Director of the National Institute for Medical Research, London, England

Increased Insulin Sensitivity in Rats with Hypothalamic Lesions and its Interpretation

B. N. SPIRTOS, M.S. (by invitation), W.R. INGRAM (by invitation), E.M. BOGDANOVE (by invitation), and N. S. HALMI (by invitation), State University of Iowa, College of Medicine, Iowa City, Iowa

Discussion opened by DWIGHT J. INGLE, The University of Chicago, Chicago, Ill.

Hypophysectomy in Patients with Malignant Diabetic Vascular Disease—Metabolic and Clinical Evaluation

LAURANCE W. KINSELL, LESTER LAWRENCE (by invitation), HARRY E. BALCH (by invitation), and R. D. WEYAND (by invitation), Samuel Merritt Hospital and the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Discussion opened by FRANCIS D. W. LUKENS, University of Pennsylvania School of Medicine, Philadelphia, Pa.

BANQUET

Saturday, June 19, 7:15 P.M.

Address by RANDALL G. SPRAGUE, President

Presentation of the Banting Medal to SIR HENRY DALE, O.M., G.B.E., M.D., F.R.S., F.R.C.P., Chairman of Trustees, The Wellcome Trust, Formerly Director of the National Institute for Medical Research, London, England

Remarks by SIR HENRY DALE
"The Changing Outlook in Medicine"

Presentation by E. PERRY McCULLAGH
"Albert and the Lion"

Special presentation for outstanding service to the American Diabetes Association to MR. HERBERT H. MARKS, Chairman, Committee on Statistics, by ALEXANDER MARBLE

SCIENTIFIC SESSION

Sunday, June 20, 9:00 a.m.

RANDALL G. SPRAGUE, Presiding

Changes in the Diabetic State after Bilateral Adrenalectomy for Diabetic Vascular Disease

JAMES T. WORTHAM and JAMES W. HEADSTREAM (by invitation), University of Arkansas School of Medicine, Little Rock, Ark.

Discussion opened by GEORGE J. HAMWI, Ohio State University College of Medicine and Ohio State University Health Center, Columbus, Ohio

An Approach to the Prediction of Diabetes Mellitus

STEFAN S. FAJANS and JEROME W. CONN, University of Michigan Medical School, Ann Arbor, Mich.

Discussion opened by RANDALL G. SPRAGUE, Mayo Foundation, Graduate School, University of Minnesota and Mayo Clinic, Rochester, Minn.

Syndrome of Essential Hyperlipemia, Mild Diabetes Mellitus and Severe Vascular Damage

DAVID ADLERSBERG, Columbia University College of Physicians and Surgeons and The Mount Sinai Hospital, and CHUN-I WANG (by invitation), The Mount Sinai Hospital, New York, N. Y.

Discussion opened by HENRY T. RICKETTS, University of Chicago, The School of Medicine, Chicago, Ill.

On the Mechanism of the Action of Insulin

DOUGLAS R. DRURY, University of Southern California, School of Medicine, and Los Angeles County General Hospital, Los Angeles, and ARNE N. WICK (by invitation), University of Southern California, School of Medicine, Los Angeles, and The Scripps Metabolic Clinic, La Jolla, Calif.

Discussion opened by HELEN E. MARTIN, University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles, Calif.

Insulin Degradation in Altered Metabolic States

NEIL J. ELGEE (by invitation), and ROBERT H. WILLIAMS, University of Washington School of Medicine, Seattle, Wash.

Discussion opened by GARFIELD G. DUNCAN, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

Autonomic Neuropathy Simulating Sympathectomy as a Complication of Diabetes Mellitus

HOWARD M. ODEL (by invitation), GRACE M. ROTH (by invitation), and F. R. KEATING, Jr., Mayo Foundation, Graduate School, University of Minnesota and Mayo Clinic, Rochester, Minn.

Discussion opened by S. GORDON ROSS, Huntington Memorial Hospital, Pasadena, Calif.

Diagnosis and Treatment of Pyelonephritis in Diabetics

G. E. JORON, J. deVRIES (by invitation), R. G. REID (by invitation), W. H. MATHEWS (by invitation), and J. W. McKAY (by invitation), McGill University and The Montreal General Hospital, Montreal, Canada

Discussion opened by HOWARD F. ROOT, Harvard Medical School and New England Deaconess Hospital, Boston, Mass.

Changes in Plasma Lipoproteins (Sf 12-20, Sf 20-35, Sf 35-100) and Cholesterol During and After Treatment of Diabetic Coma

HOWARD F. ROOT, Harvard Medical School and New England Deaconess Hospital, FRED SCHERTENLEIB (by invitation), Joslin Clinic and New England Deaconess Hospital; and GEORGE V. MANN (by invitation), Harvard Medical School, Boston, Mass.

Discussion opened by H. CLARE SHEPARDSON, University of California Medical School and the Franklin Hospital, San Francisco, Calif.

CLINICAL-PATHOLOGICAL CONFERENCE

PETER H. FORSHAM, University of California Medical School, San Francisco, and J. F. RINEHART (by invitation), University of California Medical School, and University of California Hospital, San Francisco, Calif.

SCIENTIFIC SESSION

Sunday, June 20, 2:30 p.m.

HENRY B. MULHOLLAND, Presiding

Response of Diabetic Coma to Varying Insulin Dosages

KENDRICK SMITH, University of Southern California Medical School and the Foley, McCarthy, Regan, Schade, Smith Medical Group, Los Angeles, Calif., and HELEN E. MARTIN, University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles, Calif.

Discussion opened by ALEXANDER MARBLE, Harvard Medical School and the Joslin Clinic, Boston, Mass.

Present Status of Insulin-Zinc Suspension

FRANKLIN B. PECK, Sr., and W. R. KIRTLEY, Indiana University Medical School and Indianapolis General Hospital; R. W. DYKE (by invitation), and C. E. ERNST, Indianapolis General Hospital, Indianapolis, Indiana. (Paper to be presented by Dr. Kirtley)

Discussion opened by BLAIR HOLCOMB, University of Oregon Medical School, Portland, Oregon

Observations on the Interrelationships of Exogenous Insulin and the Metabolism of Protein and Carbohydrate in Unstable and Stable Diabetes

JOSEPH L. IZZO, with the assistance of JOANNE HOFFMASTER, B.S., and ALFREDA G. SUSKIE, B.S., University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Disappearance of HGF from Insulin after Liver Perfusion

MARTIN G. GOLDNER, RAUL HERNANDEZ JAUREGUI and SHIRLEY WEISENFELD (by invitation), State University of New York College of Medicine at New York City, N. Y., and the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.

Discussion opened by STANLEY BURTON (by invitation), Mount Zion Hospital, San Francisco, Calif.

Test for Responsiveness to HGF-free Insulin as a Guide to Treatment

GEORGE E. ANDERSON, State University of New York College of Medicine at New York City, N. Y., and EUGENIE M. FRIBOURG, The Brooklyn Hospital, Brooklyn, N. Y.

Discussion opened by E. PERRY McCULLAGH, Cleveland Clinic, Cleveland, Ohio

PANEL DISCUSSION

Diabetes and Pregnancy

GARFIELD G. DUNCAN, Moderator, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

M. EDWARD DAVIS (by invitation), The University of Chicago and the Chicago Lying-In Hospital, Chicago, Ill.

LESTER J. PALMER, University of Washington School of Medicine and The Mason Clinic, Seattle, Wash.

E. STEWART TAYLOR (by invitation), University of Colorado School of Medicine, Denver, Colo.

PRISCILLA WHITE, Joslin Clinic, Boston, Mass.

BY TITLE

A Study of Urinary Tract Infections in Patients with Diabetes

KEITH R. YOUNG (by invitation), The Pennsylvania Hospital, and PERRY S. MacNEAL, Jefferson Medical College of Philadelphia and The Pennsylvania Hospital, Philadelphia, Pa.

The Treatment of Diabetic Gangrene

SAUL S. SAMUELS, Brooklyn Hebrew Home and Hospital for Aged, Brooklyn, and Stuyvesant Polyclinic, New York, N. Y.

Do We Give Too Little Emphasis to Hypoglycemia?

OLIVER E. TURNER, Mercy Hospital and St. Clair Memorial Hospital, Pittsburgh, Pa.

The Relative Rates of Fructose, Sorbitol and Glucose Oxidation in Alloxan-Diabetic Rats

ARNE N. WICK (by invitation), and JAMES W. SHERRILL, The Scripps Metabolic Clinic, La Jolla, Calif.

Stilbesterol in the Management of the Pregnant Diabetic

WILLIAM J. STEENROD, Jr., ROBERT L. REEVES and LESTER J. PALMER, University of Washington School of Medicine and The Mason Clinic, Seattle, Wash.

The Effect of Glucagon in Hepatic Glycogen Storage Disease (Von Gierke's Disease) in a 26-year-old Japanese Male with Gout and Severe Hyperlipemia

FELIX O. KOLB and J. MAX RUKES (by invitation), University of California Medical School, San Francisco, and JOHN W. GOFMAN (by invitation), University of California Medical School, Berkeley, Calif.

Histochemical Observations on Hyalinized Islets of Langerhans in Diabetes Mellitus

J. F. RINEHART (by invitation), and W. E. TORESON (by invitation), University of California Medical School and University of California Hospital, San Francisco, Calif.

Pituitary Growth Hormone and Experimental Diabetes in the Rat

FRANK L. ENGEL, MORTON BOGDONOFF (by invitation), LEONARD LISTER (by invitation), EDWARD SCHERR, and DOROTHY HOLLINGSWORTH (by invitation), Duke University School of Medicine, Durham, No. Car.

Effect of HGF-free Insulin on Blood Sugar of Liver Perfusate

STANLEY BURTON (by invitation), EDWARD D. ROBBINS, SANFORD BYERS (by invitation), SHIRLEY ST. GEORGE (by invitation), and TADASHI ISHIDA (by invitation), Mount Zion Hospital, San Francisco, Calif.

Renal Glycosuria I. Long Term Follow-up of a Case of Severe (continuous) Renal Glycosuria II. Heredity in Renal Glycosuria

S. EDWARD KING, New York University Postgraduate Medical School and University and Bellevue Hospitals, New York, N. Y.

A New Approach to the Control of Degenerative Vascular Lesions in Diabetes Mellitus

GEORGE J. HAMWI, EDWIN M. ELLISON (by invitation), JAMES M. BLOODWORTH (by invitation), and WALTER J. FRAJOLA (by invitation), Ohio State University, College of Medicine, and Ohio State University Health Center, Columbus, Ohio

The Distribution and Breakdown of Hyperglycemic Factor Labeled with I^{131}; Effect of Certain Metabolic Alterations

PAUL P. VanARSDEL, Jr., (by invitation), University of Washington School of Medicine, and ROBERT H. WILLIAMS, University of Washington School of Medicine and the King County Hospital, Seattle, Wash.

Hyperthyroidism Complicating Diabetes Mellitus. Treatment with Radioactive Iodine. Report of Twelve Cases

MAXWELL SPRING, New York Medical College, New York; Bronx Hospital, Bronx, and New York City Hospital, New York, N. Y.

Inactivation of Insulin in Vitro

HENRY H. TOMIZAWA (by invitation), HIROMICHI T. NARAHARA (by invitation), MARY LOU NUTLEY, B.A., (by invitation), and ROBERT H. WILLIAMS, University of Washington School of Medicine, Seattle, Wash.

Obesity as a Factor in the Etiology of Diabetes Mellitus with a Report of Cases

A. A. HEROLD, Sr., and A. A. HEROLD, Jr., Confederate Memorial Medical Center and North Louisiana Clinic, Shreveport, La.

Research Funds Available from the American Diabetes Association

As announced for the first time in the November-December issue of DIABETES, two fellowships of approximately $2,500 each are available for adequately trained investigators who will give their full time to a problem in the general field of diabetes in the laboratory or clinic of a recognized authority on this subject. Applications should be sent to the Executive Director, the American Diabetes Association, 1 East 45th Street, New York 17, N. Y.

New Members

The following Active Members were elected as of March 1 and April 1, 1954:

California	
Chow, Irwin D.	Fresno
Koerper, Carl W.	Oakland
Millar, Max S.	Fresno
Orson, Elliott A.	North Hollywood
Randel, Henry A.	Fresno
Wolf, George G.	Fresno
District of Columbia	
Hall, Wilson L.	Washington
Kurstin, William	Washington
Williams, William A.	Washington
Florida	
Sales, Louis M.	Jacksonville
Georgia	
Petrie, Lester M.	Atlanta
Illinois	
Albright, Arthur C.	Chicago
Fried, Julius L.	Chicago
Ingle, Dwight J., Ph.D.	Chicago
Merkel, James R.	Chicago
Seidell, Martin A.	Urbana
Indiana	
Baker, Leslie M.	Aurora
Johnson, Lonnie B.	Gary
Seaman, Charles F.	Indianapolis
Kentucky	
Kramer, Harold M.	Louisville
Michigan	
Price, Alvin E.	Detroit
Minnesota	
Goepfert, Mary	Minneapolis
Milnar, Frank J.	St. Paul
Montana	
Axley, Albert W.	Havre
New Jersey	
De Gerome, James H.	Glen Ridge
New York	
Berkson, Robert S.	Buffalo
Greene, Richard W.	Syracuse
Jivoff, Leo N.	Syracuse
Moravec, Clayton L.	Schenectady
Sanders, Martin M.	Rome
Weslock, Viola D.	Flushing
Young, Henry	New York
North Carolina	
Bishopric, George A.	Durham
Garrett, Norman H., Jr.	Durham
Sykes, Charles L.	Mt. Airy
Ohio	
Jefferies, William McK.	Cleveland
Oklahoma	
Masterson, Maude M.	Walters
Pennsylvania	
Andersen, Edwin	Pottstown
Conn, Howard F.	Uniontown
Jablonsky, Albert	Jeannette
Krosnick, Arthur	Philadelphia
Niebaum, Albert H.	Mohnton
Rumsey, John L.	Stroudsburg
South Dakota	
Grover, William W.	Yankton
Texas	
Hightower, Nicholas C.	Temple
Portman, Robert K.	Dallas
Wisconsin	
Cantwell, Roger C.	Shawano
Gilbert, Robert L.	La Crosse
Mookerjee, M. Kellogg	Milwaukee
Newman, Carl Robert	Racine
Royce, Owen, Jr.	Milwaukee
Sagi, Joseph H.	Milwaukee
Other Countries	
Argentina	
Serantes, Nestor A.	Buenos Aires
Canada	
Brassard, Paul	Roberval, Que.
Mexico	
Jauregui, Raul H.	Puebla Pue

The following Associate Member was elected as of March 1, 1954:

New Jersey	
Edwards, Marjorie, B. S.	Montclair

News of Affiliate Associations

The HOUSTON AREA DIABETES ASSOCIATION (Texas) elected the following officers in December: Mr. Orrin H. Bonney, President; James A. Greene, M.D., Vice-President; Miss Frances Low, Secretary-Treasurer. L. W. Blau, M.D., will serve as Chairman of the Committee on Detection and Education. Clinical Society officers for 1954 are: John G. Hull, M.D., President; John B. Burrows, M.D., Vice-President; R. L. Dross, M.D., Secretary-Treasurer.

The INDIANAPOLIS DIABETES ASSOCIATION elected the following officers in January: William M. Dugan, M.D., President; I. W. Wilkens, M.D., First Vice-President; Charles F. Seaman, M.D., Second Vice-President; Charles E. Test, M.D., Third Vice-President; Woodson C. Young, M.D., Secretary; and C. E. Ernst, M.D., Treasurer. Alfred T. Symmes, M.D., is Chairman of the Committee on Detection and Education, and John H. Warvel, M.D., is Chairman of the Committee on Camps.

The LEHIGH VALLEY DIABETES ASSOCIATION (Pennsylvania) elected these officers in January: W. F. Hanisek, M.D., President; Clyde H. Kelchner, M.D., First Vice-President; Raymond Wing, M.D., Second Vice-President; J. R. Dougherty, D.S.C., Secretary; and L. A. Stahl, M.D., Treasurer. W. F. Hanisek, M.D., is Chairman of the Committee on Detection and Education, and F. G. Helwig, M.D., is Chairman of the Committee on Camps. Clinical Society officers for 1954 include: W. F. Hanisek, M.D., President; Clyde H. Kelchner, M.D., First Vice-President; Raymond Wing, M.D., Second Vice-President; J. R. Dougherty, D.S.C., Secretary; and L. A. Stahl, M.D., Treasurer.

The Lehigh Valley Diabetes Association held a joint meeting with the Northampton County Medical Society March 16, at which George E. Anderson, M.D., New York City, spoke on "Functional Rehabilitation in Diabetes."

The LOS ANGELES DIABETES ASSOCIATION held its Second Annual Symposium on Diabetes in Cooperation with the Los Angeles Society of Internal Medicine on February 3. Guest speakers included Alexander Marble, M.D., Boston, Mass.; Meyer Friedman, M.D., San Francisco, Calif.; and Arne N. Wick, Ph.D., La Jolla, Calif.

Fred W. S. Modern, M.D., President of the Los Angeles Diabetes Association, presided at the afternoon Symposium on Diabetes, when the following program was presented: "Comparison of Clinical Findings with Atherogenic Index in a Group of Diabetic Patients," Louis Harris, M.D., H. Engelberg, M.D., C. Strouse, M.D., and A. Roger, M.D., presented by Doctor Harris; "Some Preliminary Studies of Pyramidine Metabolism in Diabetes," Raymond Caren, M.D., and Mortimer Morton, Ph.D., M.D., presented by Doctor Morton; "Bacteriologic Aspects of Pyelonephritis in Diabetics," William Hewitt, M.D.; "Pyelonephritis in Pregnant Diabetics," John Masson, M.D.; "Urologic Aspects of Pyelonephritis in Diabetics," Hans Zinsser, M.D.; "Carcinoma of the Liver, with Particular Reference to its Incidence in Diabetes," Hugh Edmondson, M.D.; "Difficulties in the Electrocardiographic Diagnosis of Myocardial Infarction among Diabetic Patients," Herbert B. Rubin, M.D., Murray J. Weiss, M.D., and William Paul Thompson, M.D., presented by Doctors Weiss and Thompson; "Mucopolysaccharides in Diabetes," Alexander Marble, M.D.; "Pathogenesis of Hypercholesteremia," Meyer Friedman, M.D.

Edward Shapiro, M.D., President of the Los Angeles Society of Internal Medicine, presided at the dinner meeting also held February 3. Alexander Marble, M.D., presented "The Relation of Control of Diabetes to the Development of Vascular Complications." "Metabolism in Diabetes" was presented by Douglas R. Drury, M.D., and Arne N. Wick, Ph.D.

The MICHIGAN DIABETES ASSOCIATION elected the following officers in March: Laurence F. Segar, M.D., President; Franklin W. Blaske, M.D., Vice-President; and Miss Mary M. Harrington, Secretary-Treasurer.

The Association held a dinner-meeting at the Sheraton-Cadillac Hotel in Detroit during the Eighth Annual Michigan Clinical Institute in early March. Under Association sponsorship, John H. Warvel, M.D., Indianapolis, Ind., discussed "The Treatment of Diabetic Emergencies." Alvin E. Price, M.D., and William S. Reveno, M.D., of Detroit, took part in the Arthritis Clinic March 11. G. C. Penberthy, M.D., Detroit, and

William S. Reveno, M.D., were members of the Committee on Arrangements and Program of the Institute, representing Wayne University College of Medicine and Wayne County Medical Society. Doctor Reveno also led a discussion conference March 11.

The NEW ENGLAND DIABETES ASSOCIATION presented a lecture program at Hanover, N.H., on the evening of February 26. The program included presentation of "Relation of Potassium Deficiency to Intracellular Acidosis," by Nathan A. H. Sims, M.D., Burlington, Vt.; "Daily Variations of Diabetes," by Jackson W. Wright, M.D., Hanover, N.H.; "Kimmelstiel-Wilson Syndrome in the Elderly," by Joseph L. Brandt, M.D., White River Junction, Vt.; and "Diabetes," by I. M. Rabinovitch, M.D., Montreal, Canada. A clinical conference on diabetes was arranged the following day by James Townshend, M.D., at the Veterans Administration Center, White River Junction, Vt.

The Association in cooperation with the Boston City Hospital Health Officers Association and the Diabetes Section of the U.S. Public Health Service presented a symposium on "The Metabolic Defect in Diabetes Mellitus" on March 29. Participants included Arnold Lazarow, M.D., Associate Professor of Anatomy, Western Reserve University, Cleveland; Francis D. W. Lukens, M.D., Professor of Medicine, the University of Pennsylvania School of Medicine; C. N. H. Long, M.D., Professor of Physiology, Yale University, New Haven. Alexander Marble, M.D., of the Joslin Clinic, Boston, acted as moderator of the panel discussion.

The New England Diabetes Association's Annual Meeting will be held May 10 at Boston University Medical School Auditorium. The Clinical Meeting includes: "Types of Renal Disease in Diabetes: Natural History and Diagnosis," Arnold S. Relman, M.D.; "The Pathology of the Kidney in Diabetes," Charles Sommers, M.D.; "The Incidence of Renal Disease in Diabetes and Its Relation to Diabetic Control," Alexander Marble, M.D.; "The Problem of Urinary Infections in Diabetes: Prevention and Antibiotic Management," Edward Kass, M.D.

The NEW JERSEY DIABETES ASSOCIATION held its Second Clinical Society Meeting for the 1953-54 season at the Academy of Medicine of New Jersey in Newark February 24. The Program was entitled "Management of the Pregnant Diabetic and Related Problems." William P. Given, M.D., Assistant Professor of Clinical Obstetrics and Gynecology, Cornell University Medical School, was speaker. Edward Tolstoi, M.D., Associate Professor of Clinical Medicine, Cornell University Medical School, was main discussor.

This Association elected the following officers in January: George M. Knowles, M.D., President; Everett O. Bauman, M.D., Vice-President; William Levison, M.D., Secretary; John J. Torppey, M.D., Treasurer. Otto Brandman, M.D., will serve as Chairman of the Committee on Detection and Education, and William Nyiri, M.D., as Chairman of the Committee on Camps. Elmer Sevringhaus, M.D., has been made an honorary member of the Board of Governors of the New Jersey Diabetes Association in recognition of his early and basic help to the organization in its formative years.

The NEW YORK DIABETES ASSOCIATION (Clinical Society) held a combined meeting with the New York Heart Association at Hosack Hall, New York Academy of Medicine Building, on March 9. "Cardiovascular Problems in Diabetes Mellitus" was the subject of the meeting, with Frederick W. Williams, M.D., as presiding officer. E. Perry McCullagh, M.D., Cleveland Clinic, Cleveland, Ohio, contributed "Relationship of the Control of Diabetes Mellitus to Plasma Protein Patterns and the Development of Vascular Degeneration," while Harold Rifkin, M.D., Montefiore Hospital, New York, discussed "The Kimmelstiel-Wilson Syndrome and Its Clinical Variants."

Francis D. W. Lukens, M.D., Philadelphia, Penn., addressed the Lay Society of this Association on the subject, "Recent Research in Diabetes," at the Einhorn Auditorium Theatre, New York, on January 25.

The WASHINGTON STATE DIABETES ASSOCIATION met February 25 in the Health Sciences Auditorium at the University of Washington School of Medicine, Seattle, Wash. The program, arranged for laymen, included "Diets for Diabetics," by a panel of speakers provided by the Washington Dietetic Association, and a food fair consisting of displays of low calorie foods and foods sweetened without sugar.

The BOARD OF GOVERNORS OF THE FRESNO COUNTY (California) Medical Society has approved the formation of an Affiliate Association. Leo Goodman, M.D., has been active in the development of plans for the proposed Affiliate.

News Notes

Copies of Dr. Allen's Book on "Glycosuria and Diabetes" Still Available

Copies of *Studies Concerning Glycosuria and Diabetes,* by Frederick M. Allen, M.D., published by the Harvard University Press in 1913, are available. They may be obtained without charge through the courtesy of a $1,000 grant from Eli Lilly and Company.

The book describes the production of diabetes by partial pancreatectomy, the first experimental production of hydropic degeneration of pancreatic islands and other early experimentations.

In view of the importance of the book for historic and reference purposes, preference will be given first to libraries and then to interested individuals. Requests for the book should be sent to Mr. J. Richard Connelly, Executive Director, American Diabetes Association, Inc., 1 East 45th Street, New York 17, N. Y.

Diabetes Training Center

The U. S. Public Health Service offers opportunities for training in diabetes control at the Diabetes Study and Training Center in Boston, Mass. Courses concerning group teaching of patients, the organization and management of the diabetes clinic, the relation of diabetes as a public health problem and other matters are presented. Each course is given for approximately a week. Enrollment is limited to ten individuals per course. No registration or tuition fee is required.

Courses scheduled during 1954 include: Nursing Aspects of a Public Health Diabetes Program, April 5-9; Nutritional Aspects of a Public Health Diabetes Program, May 10-14; Group Teaching of Patients, June 7-11; Diabetes Program of Public Health, September 20-24.

These courses are open to public health administrators, physicians, nurses, health educators, dietitians, nutritionists, medical technologists and medical social workers.

Application can be directed to the Diabetes Study and Training Center, U. S. Public Health Service, 639 Huntington Avenue, Boston 15, Mass.

Postgraduate Courses by American College of Physicians

These members of the American Diabetes Association are serving as officers of instruction in postgraduate courses arranged by The American College of Physicians this spring: Garfield G. Duncan, M.D., and Francis D. W. Lukens, M.D., Course No. 5, "Internal Medicine," May 10-14, at the University of Pennsylvania School of Medicine; T. S. Danowski, M.D., Course No. 6, "Diseases Due to Allergic and Immune Mechanisms," May 17-21, at the University of Pittsburgh School of Medicine; and Peter H. Forsham, M.D., Course No. 7, "Internal Medicine," June 14-18, at the University of California Medical School.

Meeting of American Geriatrics Society

The 11th Annual Meeting of the American Geriatrics Society will be held at the Fairmont Hotel in San Francisco. The scientific sessions of the meeting will begin Thursday afternoon, June 17, and continue through Saturday morning, June 19. All scientific sessions will be held in the Nob Hill Room of the Fairmont, and the annual dinner is scheduled for the Terrace Room on Friday evening, June 18.

Laurance W. Kinsell, M.D., Highland Alameda County Hospital, 2701 Fourteenth Avenue, Oakland 6, Calif., is in charge of local arrangements for the meeting.

Hebrew Medical Journal

The Editorial Office of DIABETES has received a copy of the current number of the *Hebrew Medical Journal* which marks the completion of 26 years of continuous publication of medical literature in the Hebrew language. Edited by Moses Einhorn, M.D., of New York City, the *Hebrew Medical Journal* presents to its readers articles dealing with a variety of medical subjects including tropical diseases in Israel, artificial insemination, a medieval Hebrew treatise on "Melancholy." The Fall issue included a paper by Edward Tolstoi, M.D., on "Treatment of Diabetes Mellitus by the Clinical Approach." The Editorial Office of the Hebrew Medical Journal is at 983 Park Avenue, New York 28, N. Y.

Personal

Charles H. Best, M.D., exhibited his "leisure-time" art recently at an annual exhibition of nonprofessional work done by faculty and senior members of the University

of Toronto. As reported in the *Globe and Mail,* "his landscapes are vivid, intense studies of the essentials in what he sees, with a touch of both romance and fearsomeness. Like them or not, one could have no doubt that they came from a man of powerful personality."

Barnett Greenhouse, M.D., spoke March 2 before the Lay Society of the New York Diabetes Association on "Common Errors in Diabetes." He also spoke April 2 on the new insulins at the Phi Lambda Kappa second annual interim scientific meeting at Miami Beach, Fla.

Maurice Hardgrove, M.D., Milwaukee, Wis., conducted a clinic on "Diabetes Mellitus" at the International Medical Assembly held in Chicago November 2-5, 1953.

Frederick G. Helwig, M.D., Allentown, Penn., a member of the Board of Directors of the Lehigh Valley Diabetes Association, has been appointed to the Commission on Diabetes of the Medical Society of the State of Pennsylvania. He has also received a three-year appointment to the Board of Directors of the Philadelphia Metabolic Association.

Joseph P. Hoet, M.D., Hôpital St. Pierre, Louvain, Belgium, visited the United States during the early part of the year. Following the Second Postgraduate Course at Rochester, Minn., where he spoke on "Prediabetes in Pregnancy," he lectured on various aspects of the subject at Cincinnati; the University of Pennsylvania, under the sponsorship of the Physiological Society of Philadelphia and the Hirst Obstetrical Society; the Johns Hopkins Hospital, Baltimore; the Lying-in-Hospital, Providence; and the Joslin Clinic, Boston. Before the staff of the U. S. Department of Health, Education and Welfare, and the Children's Bureau at Washington, he presented "Preventive Aspects of the Treatment of Carbohydrate Disturbances during Pregnancy." He also lectured for the joint meeting of the Clinical Society of the Diabetes Association of the District of Columbia and the Medical Society of the District of Columbia.

Robert L. Jackson, M.D., Professor of Pediatrics at the State University of Iowa Medical School, has been appointed head of the Department of Pediatrics at the University of Missouri. He will assume his new position Sept. 1, 1954.

Arnold Lazarow, M.D., of Western Reserve University School of Medicine, has been appointed Professor and Chairman of the Department of Anatomy at the University of Minnesota. He will assume his new position July 1, 1954.

Alexander Marble, M.D., of the Joslin Clinic, Boston, Mass., has been promoted to the rank of Brigadier General in the U.S. Army Reserve and appointed Commanding Officer of the 804th Hospital Center. Doctor Marble is a member of the Council of the American Diabetes Association and also a member of the Editorial Board of DIABETES.

Henry B. Mulholland, M.D., Charlottesville, Va., Chairman of the Committee on Indigent Care of the American Medical Association's Council on Medical Service, is a member of a special committee picked by the Hoover Commission's medical task force to explore the feasibility of government's utilizing insurance for provision of medical and hospital services to its beneficiaries (veterans, servicemen's dependents, mariners, Indians and others).

Herbert Pollack, M.D., New York City, heads the Committee on Nutrition established by the Council on Community Service and Education of the American Heart Association at its inaugural meeting held in conjunction with the Association's 30th Annual Meeting in Chicago. Doctor Pollack is also Consultant in Nutrition to the Surgeon General, U.S. Army.

Priscilla White, M.D., of New England Deaconess Hospital, Boston, Mass., was one of nine women physicians honored January 24 with Elizabeth Blackwell Citations. The awards have been given annually since 1949 in honor of Elizabeth Blackwell, M.D., founder of the New York Infirmary, which is celebrating its 100th anniversary. Doctor White received her citation "for her work on diabetes in childhood and during pregnancy."

The Venezuelan Government invited four American and two Cuban physicians to Caracas, Venezuela, in October 1953. Papers read at the Centro Medico Medical Society included "Recent Advances in Cardiovascular Surgery with Special Reference to the Heart," by Gerald H. Pratt, M.D., and "Recent Advances in Diabetes," by Henry Schwab, M.D.